THE INSIDER'S GUIDE TO METASTATIC BREAST CANCER

Anne Loeser

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The Insider's Guide to Metastatic Breast Cancer

by Anne Loeser

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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*

Anne Loeser
1953 - 2023

In Memoriam

This revised edition of *The Insider's Guide to Metastatic Breast Cancer* is dedicated to the memory of Anne Loeser, a visionary advocate, compassionate leader, and loving wife to Steve for 48 years. At her side during her final days was not only Steve but also Pumpkin, her cherished 29-year-old parrot, who brought her much joy.

Anne was diagnosed with metastatic breast cancer in 2011, after years of misdiagnosis fueled her determination to help others understand the complexities of the disease. Her dedication to improving the lives of patients was reflected in her founding of the Patient-Centered Dosing Initiative, a pivotal movement that led to changes in the way oncology drugs are dosed, focusing on patient well-being and quality of life.

Her tireless advocacy and the wisdom she shared in this book have touched thousands around the world. Anne's life was defined by love, and her legacy will continue to inspire those facing metastatic breast cancer.

Steve Loeser
December 2024

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Foreword by Mark E. Burkard MD, PhD

Metastatic breast cancer is a dangerous disease and it can be frightening to face alone. You are not alone. Anne Loeser is a dedicated metastatic breast cancer survivor and advocate who knows what it is like to live with metastatic breast cancer. When I decided to study exceptional people with metastatic breast cancer, I had the great fortune of meeting Anne, and have come to appreciate her knowledge, and incisive advocacy and feedback. Anne is one of the amazing people who has survived - and thrived - for years with metastatic cancer. What makes her tick?

Well, knowledge is clearly important to Anne. This book is clearly a labor of love in which deep knowledge and years of experience are shared in an organized and accessible format. This book shines in its comprehensiveness - every drug, every breast cancer subtype, every scan, every site of disease, it's there. You might read through cover-to-cover, or page to the sections relevant to you.

It is important to know that this book is updated - continuously. I ordered the book in 2019 and, months later, read and began to share some thoughts with Anne. Little did I know or expect the pace of updates and, of course, my feedback was based on an outdated edition.

As Anne tells you, always take the advice of your physician. But also advocate for yourself - and let her be your guide. This book will allow you to ask the right questions.

Mark E. Burkard MD, PhD

Professor of Medicine

University of Wisconsin—Madison

June 2, 2020

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.

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 Authors

Anne Loeser

Anne Loeser was 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 II 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-.

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.

Anne was a Project LEAD graduate, an individual member of the Metastatic Breast Cancer Alliance, a participant in Komen Greater NYC's Metastatic Advisory Committee, and co-authored a peer-reviewed ***article*** regarding Atypical Patient Responses that was printed in *Nature Partner Journal Breast Cancer* **[1, PMID:28649647]**.

Despite being a layperson with no medical background or scientific training, Anne conducted extensive research regarding MBC and its treatments. This comprehensive Guide is the result of more than 2,500 hours of effort spanning 7 years.

The Insider's Guide to Metastatic Breast Cancer provides comprehensive information that will enable you to work effectively with your medical team in order to attain the best possible outcome and quality of life.

Anne passed away on October 10, 2023, from complications of MBC and GI issues. To continue Anne's legacy and with Anne's blessing prior to her death, the Metastatic Breast Cancer Alliance has taken on the task of updating the Insider's Guide to Metastatic Breast Cancer with contributions from the below co-authors, all of whom are living with MBC.

Amy Beumer, PhD

Amy was diagnosed with stage I breast cancer as well as extensive ductal carcinoma in situ (DCIS) in 2017 at the age of 38. After treatment she went back to her life as a newly married assistant professor, teaching biology and conducting research in microbiology and team learning. But things change, and she was diagnosed with a pleural effusion and other distant metastases in 2020. Progression on the first drug regimen was rapid, and this led to her retirement from academia and immersion into first the science and community of MBC and then advocacy.

Amy's advocacy efforts have been diverse and include legislative, peer-to-peer support and mentoring, and of course research and

education. The latter two are her passions and where she thinks she can make the biggest difference, utilizing the skills she gained professionally as both a scientist and an educator. She serves on the leadership team of Project Life, coordinating science and education, including an MBC workshop series. She is also an active member of the Patient Centered Dosing Initiative, working to increase our knowledge about dosing in the MBC sphere. Amy reviews research grants for METAvivor, as well as serving on the board in various capacities. She is honored to work with other advocates on updating Anne's book.

Janice Cowden, RN

Diagnosed with stage IV triple negative breast cancer in 2016, five years after an early-stage breast cancer diagnosis, Janice launched into patient advocacy following training through Living Beyond Breast Cancer's Hear My Voice outreach program in 2017. As a peer-to-peer support and research patient advocate, Janice is passionate about supporting others with MBC, in addition to continually furthering her scientific knowledge base of this disease, treatments, and clinical trials. Her professional life as a pediatric nurse (retired) and professional pharmaceutical sales representative fuels her passion for scientific learning and dissemination of the most up to date disease-related information, which she acquires through attending evidence-based breast cancer conferences and webinars.

Janice works with several patient-founded and -led organizations including PCDI, GRASP, and Project Life MBC. As a trained peer support volunteer, she is founder of an international online peer support group for patients newly diagnosed with MBC. She serves on the board of directors for Metavivor Research and Support, Inc., and is an advisory board member for Project Life MBC. In 2022, she attended ASCO as a patient advocate scholarship recipient. In October 2022, she was invited to serve as a lead patient advocate, representing PCDI, on a research study with ASCO. When she's not busy with advocacy work, Janice enjoys traveling, reading, outdoor activities, and spending time with family, including her husband, two adult children and three grandchildren.

Kelly Shanahan, MD

In 2008, Kelly Shanahan had everything going for her: a busy and successful OB-GYN practice; a precocious 9-year-old daughter; and a well-used passport from traveling all over the world with her family to attend conferences, with a liberal dose of vacation on the side. When

she was diagnosed with stage IIB breast cancer, she considered it a mere bump in the road.

And for 5 years, breast cancer was an aside, something to put in the past medical history section of forms. Even when she developed sudden back pain, Kelly never thought it could be breast cancer rearing its ugly head – a pulled muscle, a herniated disc maybe, but not what it turned out to be: MBC in virtually every bone in her body, with a fractured vertebrae and an about-to-break left femur. Kelly was diagnosed in 2013, on her 53rd birthday.

Neuropathy from the chemo cost Kelly her career, but she has found a new purpose in advocacy. Kelly is president of the board of directors of Metavivor, a member of the Metastatic Breast Cancer Alliance, a Komen Advocate in Science, a grant reviewer, and research advocate. She is passionate about getting patients to the table in the design, implementation, and follow up of clinical trials. Follow her on twitter and Bluesky @stage4kelly.

Kelly Shanahan is a mother, a wife, a daughter, a doctor, a woman living with metastatic breast cancer.

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 authors have endeavored to provide information about approved treatments in the US, Canada, Europe, and Australia. That said, in some instances non-US treatment options are ambiguously worded, and US-based media may not write about therapies that are newly approved in other countries. Therefore, it's possible that some treatment options outside the US have been inadvertently omitted, and patients are encouraged to work with their medical teams to identify all applicable treatment options in their country.

Information about specific diets has been deliberately excluded, since there are nearly as many perspectives and opinions as there are MBC patients! Diet is an emerging area of investigation, and randomized clinical trials are testing the role of diet in response to treatment and management of side effects in people with MBC. Be sure to check with your doctor before beginning any new diet.

And now a word of encouragement! The average survival time has doubled for patients with hormone receptor- positive metastatic breast cancer, and also for patients with HER2+ metastatic breast cancer. In the past decade the median survival for these two subtypes has risen from just 1 or 2 years to 5 years. This means that half of patients with these cancers may live for more than five years, with some living for as long as 10 years (or even more). **From:**

https://medicalxpress.com/news/2021-11-average-survival-patients-advanced-breast.html

Readers may find the following chapters 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/HER2- MBC & Related Therapies

HER2+/Hormone Receptor Negative MBC & Related Therapies

Triple Negative MBC & Related Therapies

Hormone Receptor Positive/HER2+ MBC & Related Therapies

Male MBC

Approved Therapies for Patients with BRCA Mutations

Approved Therapies Based Upon Tumor Characteristics

MBC Conventional Therapies Overview

Research and Potentially Helpful 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 manage them if they arise.

9. All too often, quality of life issues are underreported and/or overlooked. Therefore, it is extremely important that patients living with MBC obtain the best possible degree of comfort. To this purpose, consider speaking with your doctor about obtaining palliative care, which is designed to help people with a serious illness maximize their comfort level as much as possible. Palliative care differs from hospice care in that you do not need to be anywhere near end of life, and you can continue to receive standard treatment while on palliative care. Palliative care should be obtained soon after diagnosis, although it can be requested at any time. As per Cure Magazine's winter 2019 publication, a study of 2,307 records of advanced cancer patients determined that those who received outpatient palliative care survived 4.5 months longer than those who did not. (The chapter about *Palliative Care* describes this type of care in more detail).

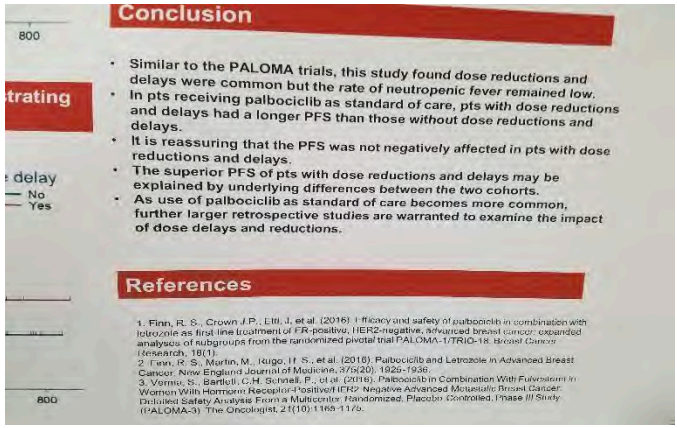
10. Irrespective of whether you are receiving palliative care, if you're experiencing pain, discomfort, or other problems, inform your medical team accordingly. If the initial remedy is ineffective, request another (or stronger) option. Continue this process until the prescribed medication or therapy successfully works, or until it works well enough that you are able to live with it.

11. If you are 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:** ***http://cdn2.hubspot.net/hub/1670/file-983271054-pdf/Tatiana_Prowell_(1).pdf?t=1449608504236***

The degree of treatment-related side effects may be related to body mass index (BMI) since it's possible that patients with a lower BMI experience more significant side effects with regard to certain drugs. Therefore, patients with lower BMIs may wish to discuss possible dosage reduction with their doctor. **From:** ***https://www.healio.com/hematology-oncology/breast-cancer/news/online/%7B162968a8-3b60-4ad8-9142-45fe5c5f2db5%7D/bmi-inversely-associated-with-palbociclib-induced-neutropenia***

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. 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.

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) can be leveraged for reducing chemotherapy-induced nausea and vomiting. **From:** ***https://www.sciencedaily.com/releases/2018/06/180612092128.htm***

14. If you will be taking hormonal therapy or certain types of chemotherapy, it's possible that you may lose some or all of your hair. This condition, known as alopecia, can be treated with topical (or possibly oral) minoxidil in patients undergoing hormonal therapy, and with the FDA-approved DigniCap and Paxman scalp cooling systems in patients undergoing chemotherapy. If you're concerned about hair loss, speak with your doctor about the effectiveness of these therapies (and possibly additional options such as Vitamin C supplements), and ascertain whether they are covered by insurance. **From:** ***https://www.cancer.org/treatment/treatments-and-side-effects/physical-side-effects/hair-loss/cold-caps.html*** and ***https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4864803/#Sec3title***

15. It's advisable to consult with your dentist before and throughout treatment and - time permitting - to get as much dental work completed as possible before treatment begins. This is because some cancer treatments can increase vulnerability to infections and/or directly affect oral health. It's also important to keep your dentist apprised of your cancer-related therapy, and to let your medical team know about any major dental procedures that you'll be undergoing.

16. Similar to the above, if you require immunizations, it's advisable to work with your medical team to obtain them in advance of your treatment if time permits.

17. Washing hands frequently may help you avoid infection while on treatment. This includes washing hands when you come home, before and after brushing teeth, before and after eating, and before and after going to the bathroom.

18. Obtaining adequate hydration is important for maintaining health and well-being. If your urine is a dark-yellow color, it's a sign that you need to drink more liquids.

19. Ask your medical team what phone number to call if a medical emergency arises after business hours.

20. As a general guideline, if you run a fever of 100.5 or higher, call your health care provider immediately.

21. If warranted, consider asking your medical team about obtaining the services of a Patient Navigator or a Nurse Navigator who might assist you with regard to medical or non-medical issues such as insurance and disability.

22. 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.

23. 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.

24. 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.

25. If you are a young woman or man living with MBC, you might not have been made aware that treatment may cause infertility issues. For patients facing the decision about having children following their MBC diagnosis, early intervention is crucial because fertility preservation efforts need to occur before cancer treatment begins. Therefore, these patients should speak with their doctors about how quickly their cancer-related therapy must be initiated. It is also necessary to find out whether insurance will cover fertility-related procedures. Options for young women include: 1) egg banking (whereby their eggs are extracted and frozen), 2) embryo banking (a procedure involving injections to increase egg production, subsequent egg extraction and combination with sperm, freezing the fertilized eggs, and implantation at a later date), and 3) ovarian tissue cryopreservation whereby the ovary is removed, tissue is frozen, and eventually implanted. Young men may use sperm banking (if there is no sperm in the ejaculate, a surgical biopsy of the testes called Testicular Semen Extraction might be considered). In addition to speaking with Medical Oncologists and reproductive endocrinologists, patients hoping to have children may contact the Oncofertility Consortium at 1.866.708.3378. **From:** ***https://www.oncnursingnews.com/publications/oncology-nurse/2011/november-2011/oncofertility-updates-on-fertility-preservation-related-to-cancer-care***

26. 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).

27. 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.

28. 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!

29. 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 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.

30. 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.

31. 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 palbociclib (Ibrance) and fulvestrant (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).

32. 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.)*

33. 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.

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

35. Because it doesn't show up as a solid tumor and looks more like a spider web, lobular metastatic breast cancer may be 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.

36. If you will be taking the chemo drugs capecitabine (Xeloda) or 5-FU, you may want to speak with your doctor about getting tested for specific mutations in the dihydropyrimidine dehydrogenase (DPD) 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. Although this test is not considered the standard of care, it may nevertheless be worth

discussing with your healthcare provider. The FDA recently approved new labeling regarding 5-FU for injection and DPD deficiency.
https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-safety-labeling-changes-regarding-dpd-deficiency-fluorouracil-injection-products

37. Since chemotherapy and various targeted therapies such as trastuzumab (Herceptin) 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.

38. If you will be taking fulvestrant (Faslodex) injections - which involve a thick (viscous) liquid that can cause discomfort when injected - it helps to warm the vial under the armpit until it reaches body temperature before injecting. Additionally, the shot should be administered slowly over a period of 1 – 2 minutes. (Additional information about fulvestrant (Faslodex) injections is located under *Hormone Receptor Positive/HER2- MBC & Related Therapies).*

39. 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.

40. If you're a "de novo" patient who was diagnosed with MBC without previously having early stage breast cancer, research remains controversial about whether surgery to remove the primary tumor may help extend survival. One study found a survival benefit and another did not, so patients are encouraged to discuss the benefits and risks of surgery with their physicians. **From[3]:** ***http://www.eurekalert.org/pub_releases/2016-06/uops-itc060116.php*** and ***https://www.eurekalert.org/pub_releases/2020-05/ecrg-sar052820.php***

41. Discuss your wishes regarding the type of care you do and do not want in the event that at some point you are unable to speak for yourself. Specific documents such as an Advance Health Care Directive/Living Will, POLST or MOLST (depending upon your

state of residence), Do Not Resuscitate, Do Not Intubate, and any other relevant papers should be completed and appropriately filed. You should clearly designate Health Care Agent(s) who will speak on your behalf if you are unable to do so.

42. 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/***

43. 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 n**on-invasive** or i**nvasive:**

- **Non-invasive** b**reast 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.

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

  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 the milk ducts 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 the milk lobules 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 bloodstream 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 subtypes 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. Patients diagnosed with IBC are either Stage III (due to skin involvement) or Stage IV if the cancer has metastasized to distant organs.

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 receptor and progesterone receptor positive and HER2- (although it may harbor a HER2 and/or HER3 mutation) and appears to derive particular benefit from treatment with aromatase inhibitors (such as letrozole) compared with tamoxifen. **From[4, PMID:27022119]**

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, FDG PET scan, FES PET scan, 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, it 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 **[5, 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 ILCs, 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[6, PMID:24168512]**

In general, ILC breast cancers are hormone receptor positive, HER2-, 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, patients with ILC appear to respond better to aromatase inhibitors (such as letrozole (Femara)) than to tamoxifen (Nolvadex). Patients with ILC may wish to speak with their medical teams about abemaciclib (Verzenio), which appears to be particularly effective in treating MBC that has spread to the abdominal area. A notable subset of ILC cancers contain a *FGFR* mutation for which targeted drugs are being tested in the clinical trial setting as of January 2020. **From[7, PMID:23270564]:** ***https://jeccr.biomedcentral.com/articles/10.1186/1756-9966-31-103*** and ***https://www.fiercepharma.com/pharma/esmo-lilly-s-verzenio-looks-for-edge-gold-standard-data-tough-to-treat-patients***

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:** ***https://pubmed.ncbi.nlm.nih.gov/30423024/***

Patients with ILC may be interested in visiting the 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 of 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***

MBC SUBTYPE AND TESTING OVERVIEW

Tumor tissue from MBC patients must be tested to determine the patient's **disease subtype** based upon hormone receptor status (either positive or negative) and HER2 status (positive or negative). There are four official disease subtypes, and the treatments for each subtype varies:

1. **Hormone Receptor Positive, HER2-** (which is the most common subtype): This subtype is referred to as either "Luminal A" if there is a low Ki67 score, or "Luminal B" if there is a higher Ki67 score. (Ki67 is an antigen, or protein, that sits on the surface of a cell and stimulates the production of an antibody. The usual Ki67 index cut point to distinguish luminal B from luminal A tumors is 13.25%).

2. **HER2+, Hormone Receptor Negative:** This subtype is usually referred to as "HER2+."

3. **Triple Negative ("TNBC"):** Both the hormone receptor status and the HER2 receptor status are negative. This subtype is sometimes referred to as "Basal Like."

4. **Hormone Receptor Positive and HER2+** (sometimes referred to as Triple Positive): This subtype is also referred to as "Luminal B,"

which can be confusing because some Hormone Receptor Positive, HER2- breast cancers are also referred to as Luminal B as described above.

HER2 Low: Although HER2 low is not an official subtype, many patients who are hormone receptor positive and HER2- and many patients who are triple negative have cancer with a low level of HER2 expression, defined as an immunohistochemistry (IHC) value +1 or +2 and negative for HER2 gene amplification by in situ hybridization (ISH). Whereas these levels of HER2 are still considered to be HER2-, they fall within the HER2 low category. Notably, the drug fam-trastuzumab deruxtecan-nxki (T-DXd; Enhertu) has been FDA approved for MBC patients with HER2-low or -ultralow expression who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy.

Tumor tissue is also used for biomarker **testing** to determine whether the cancer has a *PIK3* mutation and/or microsatellite instability (a genetic predisposition to mutation that results from impaired DNA mismatch repair), in which case therapies are available as described in the chapter *"Approved Therapies Based Upon Tumor Characteristics."*

Patients' **blood ("liquid biopsy")** can also be used in a similar manner as somatic gene testing, above. Liquid biopsies spare the patient from the discomfort of tumor biopsies, and can be repeated to identify mutations that have developed over time. Liquid biopsy testing may also be used to determine whether an individual has developed resistance to therapy (such as an *ESR1* mutation, which can signify resistance to aromatase inhibitors), or is eligible for a clinical trial that requires a specific mutation or biomarker.

Lastly, MBC patients' **blood or saliva can be used for genetic testing** to determine whether the patient has a familial (inherited) mutation in genes, such as *BRCA1*, *BRCA2*, and/or *PALB2*. HER2- MBC patients with *BRCA* mutations are eligible for treatment called "PARP Inhibitors" (olaparib (Lynparza) or talazoparib (Talzenna)), which are also being tested with encouraging results on MBC patients with *PALB2* mutations.

TESTING FOR HORMONAL AND HER2 STATUS

When breast cancer cells are found, the tests listed below will be undertaken in order to determine hormonal receptor positivity (specifically, estrogen receptor positivity [ER] and progesterone receptor positivity [PR]), along with HER2/neu positivity. The outcome will help to determine the type of treatment(s) the patient will receive:

Hormone Receptor (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 and/or progesterone, 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, which uses tumor tissue, 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 ER and/or PR 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 is present.

"2" means that a moderate number is present, and "3" means that a large number is 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."

ASCO 2020 Guidelines state that all tumor specimens with at least 1% tumor cell nuclei immunoreactive for ER or PR are considered hormone receptor positive, with the caveat that tumors with 1% to 10% of tumor cell nuclei immunoreactive for ER should be reported as "ER-low positive" and that tumor specimens with less than 1% tumor cell nuclei immunoreactive for ER or PR are considered hormone receptor negative. **From: *https://www.cancertherapyadvisor.com/home/cancer-topics/breast-cancer/breast-cancer-update-asco-cap-guideline-no-sweeping-changes***

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[8, PMID:21037871]:**

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[8, PMID:21037871]:** ***http://www.breastcancer.org/symptoms/testing/types/ihc***

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 receptor positivity, the study found a gene signature that was consistent with ER-positive status. **From[9, PMID:22291085]: *http://jco.ascopubs.org/content/30/7/729.long***

Testing for Whether Breast Cancer is HER2+ or HER2-:

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. There are four possible tests for HER2, all of which use tumor tissue:

1. **FISH** (**F**luorescence **I**n **S**itu **H**ybridization (FISH)) **Test:** The FISH 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**mmunohistochemistry (IHC)): The IHC 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 Dual In Situ Hybridization (**Inform HER2 Dual ISH Test**): 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. **S**ubtraction **P**robe **T**echnology **C**hromogenic **I**n **S**itu **H**ybridization (SPoT-Light HER2 CISH Test): 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).

NOTE: Results of 1+ or 2+ (with negative results on in situ hybridization) indicate that although the HER2 status is officially negative, it is considered **"HER2 low."** If the result is IHC 0 with membrane staining, the cancer is considered **"HER2 ultralow."** The drug fam-trastuzumab deruxtecan-nxki (T-DXd; Enhertu) has been approved to treat patients with HER2-low and –ultralow status.

If the results are 3+, or 2+ with positive results on in situ hybridization, the cancer is considered **"HER2+."**

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[10, PMID:PMC2793708]: ***https://dailynews.ascopubs.org/do/asco-cap-guideline-update-confirms-previous-recommendations-her2-testing-breast-cancer***

ASCO guidelines specifically define HER2+ 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[10, PMID:PMC2793708; 11,**

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+, or 2+ with positive results on in situ hybridization, FISH positive, SPoT-Light HER2 CISH positive, or Inform HER2 Dual ISH positive respond to the medicines that target HER2+ breast cancers.

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[11, PMID:24101045]:**

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.

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*).

7. Hormone Receptor-Positive/HER2- MBC & Related Therapies

The National Comprehensive Cancer Network (NCCN) provides guidelines for treatment of people with MBC. The patient version can be found here: ***https://www.nccn.org/patients/guidelines/content/PDF/stage_iv_breast-patient.pdf***. More information is available in the professional guidelines: (***https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf***).
You can create a free account to view the professional guidelines. The information provided below is current as of 2023. Please see the above guidelines for the most recent updates.
In addition, the American Society of Clinical Oncology (ASCO) also provides guidelines.

Hormone receptors are present in the majority of 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 referred to as hormone receptor positive (HR+) unless their cancer is also HER2+ (called "Triple Positive"), for which distinct treatment guidelines exist as described in the chapter entitled, "*Hormone Receptor Positive/HER2+ MBC & Related Therapies."*

Patients with the subtype 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- (but with a high Ki67 score, unlike Luminal A breast cancer).

International guidelines state that for hormone receptor-positive (HR+) human epidermal growth factor receptor 2-negative (HER2-) MBC patients, endocrine (hormonal) therapy in conjunction with a CDK4/6 inhibitor should be given as first-line treatment, except in case of acute visceral crisis (severe organ dysfunction). ***https://society.asco.org/sites/new-www.asco.org/files/content-files/practice-patients/documents/2024-Resource-Stratified-Summary-Recommendations.pdf***

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[14, PMID:27217461]:** ***http://www.medscape.com/viewarticle/864032?src=wnl_edit_tpal&uac=68373MK***

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 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: Endocrine-based therapy is often continued in the second- and third-line setting unless a germline "inherited" *BRCA* mutation exists (in which case a PARP inhibitor [olaparib (Lynparza) or talazoparib (Talzenna))] can be prescribed, or a somatic "tumor" *PI3K* mutation exists (in which case the PIK3-directed drug called alpelisib (Piqray) can be prescribed), with chemotherapy deferred until the tumor becomes endocrine therapy refractory and/or a visceral crisis in imminent. At this point, other options such as chemotherapy (or potentially clinical trials) should be considered. **From:** ***https://www.scholars.northwestern.edu/en/publications/advances-in-endocrine-therapy-for-postmenopausal-metastatic-breas***

TYPES OF HORMONAL (ENDOCRINE) THERAPY DRUGS:

- **Aromatase Inhibitors (AIs):** Aromatase inhibitors (AIs) are taken in pill form and work by blocking the enzyme "aromatase," which turns 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. There are currently three FDA-approved AIs: **letrozole (Femara), anastrozole (Arimidex),** and **exemestane (Aromasin).** Letrozole (Femara) and anastrozole (Arimidex) are "non-steroidal" AIs, which reversibly bind to the aromatase enzyme. Anastrozole (Aromasin), the steroidal AI, binds to aromatase irreversibly. Despite this slight difference in the mechanism of action,

non-steroidal and steroidal AIs are very potent inhibitors of aromatase and have been shown to decrease estrogen levels to below the level of detection. 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 (Femara) appears to be a more potent suppressor of total-body aromatization and plasma estrogen levels compared with anastrozole (Arimidex), so this should be taken into consideration when beginning hormonal treatment with an AI. **From[16, PMID:14556923; 17, PMID:11821457; 18, PMID:12775735]: *http://www.medscape.org/viewarticle/434229***

- **Selective Estrogen Receptor Modulators (SERMs):** SERMs are taken in pill form and work by attaching to the estrogen receptors on the surface of cells, where they block the effects of estrogen. Currently there are two FDA-approved SERMs specifically used to treat metastatic breast cancer: **tamoxifen (Nolvadex)** and **toremifene (Fareston**). Tamoxifen (Nolvadex) is more widely used than toremifene (Fareston) in the US, although for premenopausal patients with flaws in their CYP2D6 genetic pathway, toremifene (Fareston) is a better choice than tamoxifen (Nolvadex) because it does not rely on this pathway to be effective (more about tamoxifen (Nolvadex) and CYP2D6 under *Possible Causes for Hormonal Therapy Resistanc*e in this chapter). Note that in premenopausal patients, medical suppression of the ovaries with a luteinizing hormone-releasing hormone (LHRH) agonist described below was found to be better when added to tamoxifen (Nolvadex) than tamoxifen alone.

  A subset of individuals with MBC may experience a "flare" of their breast cancer within two days to three weeks after starting tamoxifen (Nolvadex). 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 4 to 6 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

- **Selective Estrogen Receptor Downregulators or Degraders (SERDs):** Selective estrogen receptor downregulators or degraders (SERDs) bind to the estrogen receptor in competition with estrogen in the body. Once the SERD binds to the site, it causes the receptors to break down, thereby preventing normal cellular response to estrogen. **Fulvestrant (Faslodex)** is administered as two intramuscular injections (one in each cheek of the buttocks). In January 2023, the FDA approved elacestrant (Orserdu), the first oral SERD, as second-line treatment for postmenopausal women or men with ER+, HER2- MBC with a mutation in the gene for the estrogen receptor, called *ESR1*. This mutation can be detected with an FDA-approved companion diagnostic test. From: ***https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-elacestrant-er-positive-her2-negative-esr1-mutated-advanced-or-metastatic-breast-cancer***

- **Estrogen (Ethinyl Estradiol):** Ethinyl estradiol is an oral medication that 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 devoid of estrogen exposure for a considerable amount of time because they have been postmenopausal for at least 5 years or due to long-term anti-estrogen treatment. (More about this in the *Hormonal Therapy* section of this document).

- **Megace (Megestrol Acetate):** Megace, an oral drug**,** 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:** ***https://www.breastcancer.org/drugs/megace***

- **Fluoxymesterone (Halotestin): Fluoxymesterone (Halotestin)** is an oral 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, fluoxymesterone (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.

DRUGS USED IN COMBINATION WITH HORMONAL THERAPY MEDICATIONS

Hormonal therapy drugs can be administered alone, or in some cases, in combination with other drugs, and hormonal therapy in combination with a CDK4/6 inhibitor is now the standard-of care as initial treatment for hormone receptor-positive, HER2- MBC patients.

- **CDK4/6 Inhibitors:** Cancers can grow uncontrollably because their cells are able to overrun the molecular brakes that normally permit cells to divide only when absolutely necessary. These brakes are regulated by a group of enzymes known as "cyclin-dependent kinases" (CDKs). Alterations causing overactivity of two of these enzymes, CDK4 and CDK6, are found in a variety of cancers, including breast cancer. CDK4/6 inhibitors, which are taken orally, are designed to interrupt the uncontrolled growth of cancer cells. There are currently three FDA-approved CDK4/6 inhibitors, also referred to as "targeted therapies," for MBC: **palbociclib (Ibrance), ribociclib (Kisqali),** and **abemaciclib (Verzenio).**
  In 2022, it was determined that first-line palbociclib (Ibrance) with letrozole (Femara) did not confer an overall survival (OS) benefit, although the analysis was hindered by missing data. After a median 90 months of follow-up, the median OS was 53.9 months among patients receiving palbociclib (Ibrance) plus letrozole (Femara) vs. 51.2 months among patients given placebo plus letrozole**.** **From:** ***https://oncology.medicinematters.com/asco-2022/breast-cancer/paloma-2-survival-benefits-unclear-palbociclib-abc/23129540***

  The overall survival (OS) conferred by ribociclib (Kisqali) (in combination with fulvestrant (Faslodex)) appears to be highly favorable. Based upon an updated exploratory OS analysis of the Phase 3 MONALEESA-3 study, the combination of ribociclib (Kisqali) and fulvestrant (Faslodex) achieved a median OS of 67.6 months in the first-line setting for postmenopausal patients with

HR+/HER2- advanced or metastatic breast cancer. **From:** ***https://www.targetedonc.com/view/ribociclib-demonstrates-promising-os-benefit-in-hr-her2--advanced-breast-cancer***

Furthermore, ribociclib (Kisqali) plus endocrine therapy appears to be more effective than chemotherapy in the first-line setting for patients with rapidly progressing and/or symptomatic organ disease. The RIGHT Choice trial of 222 MBC patients, most of whom had symptomatic visceral disease, compared ribociclib (Kisqali) plus endocrine therapy to combination chemotherapy in the first-line setting and determined that the median progression-free survival was significantly longer in the ribociclib (Kisqali)/endocrine therapy arm than in the chemotherapy arm (24.0 months vs.12.3 months). **From:** ***https://www.cancertherapyadvisor.com/home/news/conference-coverage/san-antonio-breast-cancer-symposium-sabcs/sabcs-2022/breast-cancer-metastatic-ribociclib-endocrine-therapy-outperforms-chemo/***

However, unlike palbociclib (Ibrance) and abemaciclib (Verzenio), ribociclib (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). For patients suffering less severe side effects, an assessment of patients in the MONALEESA study determined that dose reduction did not compromise response to treatment, and most patients needed only one dose reduction to relieve their symptoms.

The OS conferred by abemaciclib (Verzenio) and an aromatase inhibitor (AI) in the first line setting is also noteworthy. As reported at SABCS 2023 (GS01-12), based upon the Phase 3 MONARCH-3 study (NCT02246621), after 8 years of follow-up, patients taking the combination abemaciclib (Verzenio) and an non-steroidal AI as initial treatment achieved a median overall survival of 66.8 months compared with a median of 53.7 months for patients taking an AI only, a difference that was not statistically significant. The median progression-free survival difference was significant: 29.0 vs 14.8 months, respectively. **From:** ***https://www.healio.com/news/hematology-oncology/20220915/abemaciclib-regimen-shows-further-signs-of-benefit-in-advanced-breast-cancer-subgroup and***

https://ascopost.com/news/december-2023/abemaciclib-plus-ai-in-postmenopausal-patients-with-advanced-breast-cancer-final-overall-survival-analysis-from-monarch-3/

At SABCS 2022 in Poster Spotlight Discussion 13: Therapeutic Approaches for HR+/Her2- Breast Cancer, it was disclosed that abemaciclib (Verzenio) offers a pronounced benefit in subgroups associated with a poorer prognosis such as visceral disease, primary resistance to endocrine therapy, or negative progesterone receptor status.

As reported at ASCO 2023 (LBA1000), the SONIA trial (NCT03425838) showed no difference in the time to progression or survival when a CDK4/6 inhibitor was used as a first-line therapy compared with as a second-line therapy. However, use in the first-line setting was associated with greater toxicity and greater costs because patients remained on the drug longer in the first-line setting. From:
https://dailynews.ascopubs.org/do/sonia-challenges-need-first-line-use-cdk4-6-inhibitor-hr-positive-her2-negative and https://meetings.asco.org/abstracts-presentations/219701

It is advised that oncologists and patients consider the toxicity profile, quality of life, drug interactions, and individual patient preferences when deciding which CDK4/6 inhibitor to treat the patient with.

As is the case with other oncology drugs, it is not uncommon for a patient's cancer to become resistant to CDK4/6 inhibitors over time. A key biomarker associated with CDK4/6 resistance is the development of an *RB1* (retinoblastoma gene 1) mutation.

- **Mammalian Target Of Rapamycin (mTOR) Inhibitors**: Mammalian Target Of Rapamycin (mTOR) inhibitors, which are taken orally, block the activity of the "mammalian target of rapamycin." mTOR is a kinase, a type of protein in the body. Kinases help all cells - both healthy and cancer cells - get the energy they need. When kinases are overactive, they help certain breast cancers to grow. mTOR inhibitors work by interfering with the mTOR kinase, thus stopping cancer cells from getting the

energy they need to grow. Currently there is one FDA-approved mTOR inhibitor (also referred to as a "targeted therapy") for MBC patients called **everolimus (Afinitor).**

- **PI3K Inhibitors:** The "phosphoinositide 3-kinase" (PI3K) signaling pathway controls a wide variety of cellular processes, including cell death and survival, cell migration, protein synthesis and metabolism. When there is a *PIK3CA* mutation, there is corresponding activation of the PI3 kinase pathway, which leads to cancer progression and resistance to endocrine therapy. **Alpelisib (Piqray)** is an oral PI3K inhibitor that is FDA- and EU- approved for the treatment of hormone receptor-positive, HER2- postmenopausal MBC patients (including men) with *PIK3CA* mutations, and it is **used in combination with fulvestrant (Faslodex)** when prescribed. In November 2023, the FDA approved capivasertib (Truqap) plus fulvestrant (Faslodex) as second-line treatment for HR+, HER2- MBC with alterations in the genes *PIK3CA*, *AKT1*, and/or *PTEN*. These alterations can be detected with an FDA-approved companion diagnostic test. From: ***https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-capivasertib-fulvestrant-breast-cancer*** In October 2024, the FDA approved inavolisib (Itovebi) plus palbociclib (Ibrance) and fulvestrant (Faslodex) as first-line treatment in the metastatic setting for hormone-resistant, *PIK3CA*-mutated, hormone receptor-positive, HER2- MBC. Inavolisib (Itovebi) and palbociclib (Ibrance) are oral therapies (pills), whereas fulvestrant (Faslodex) is two shots received once every 4 weeks. An FDA-approved companion diagnostic test (FoundationOne CDx) was also approved for identifying patients with *PIK3CA* mutations. The approval of this drug combination was based on the INAVO120 study (NCT04191499), which enrolled 325 patients. Patients were randomized to receive inavolisib (Itovebi) in combination with palbociclib (Ibrance) and fulvestrant (Faslodex) or placebo, palbociclib (Ibrance), and fulvestrant (Faslodex). Progression-free survival (PFS) was 15.0 months in the inavolisib (Itovebi) group compared with 7.3 months in the placebo group (SABCS 2023, Abstract GS03-13). Additionally, adding inavolisib (Itovebi) to fulvestrant (Faslodex) and palbociclib (Ibrance) in the

first-line setting extended PFS compared to fulvestrant (Faslodex) and palbociclib (Ibrance) alone (24.0 months with inavolisib (Itovebi) vs 15.1 months without) (ASCO 2024, Abstract #1003). Overall survival data are not yet available. Side effects such as high blood sugar (hyperglycemia), which was experienced by 59% of patients, diarrhea (48%), rash (25%), and mouth sores (51%) were resolved with standard interventions, did not lead to inavolisib (Itovebi) dose reduction or interruption, and were mostly grade 1-2 (mild) with some more serious grade 3 effects (however, there were no grade 4-5). From: ***https://www.gene.com/media/press-releases/15012/2023-12-08/genentechs-inavolisib-combination-reduce and https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-inavolisib-palbociclib-and-fulvestrant-endocrine-resistant-pik3ca-mutated-hr-positive*** and ***https://www.nejm.org/doi/full/10.1056/NEJMoa2404625***

- In premenopausal women – and also in men - a **luteinizing hormone-releasing hormone (LHRH)** agonist such as **goserelin (Zoladex), leuprolide (Lupron),** or **triptorelin (Trelstar)** is recommended along with hormonal (endocrine) therapy. In females, LHRH agonists work by telling the pituitary gland located in the brain to stop producing luteinizing hormone (which stimulates the ovaries to release estrogen). This process of limiting the production of estrogen is referred to as "ovarian suppression." **In males, these LHRH drugs are sometimes referred to as gonadotropin-releasing hormone (GnRH)** agonists, which suppress the testicular production of estrogen. All three medications are administered as injections and should generally be used by hormone receptor-positive men and premenopausal women in combination with hormonal therapy. *(Instead of initially taking an LHRH agonist, some hormone receptor-positive premenopausal patients may opt to undergo an oophorectomy, which involves the surgical removal of both ovaries - referred to as "ovarian ablation" - at which point they become postmenopausal and would follow the endocrine treatment guidelines for postmenopausal women).*

- Patients with **bone metastases** should receive bone-directed therapy such as **denosumab (Xgeva or Prolia),** which is given by injection**,** or **zoledronic acid (Zometa),** which is administered by infusion, in addition to their cancer-directed therapy. These drugs help to prevent fractures and other cancer-related bone problems in adults with cancer that has spread to the bones.

OTHER DRUGS

- Patients with inherited ("germline") *BRCA* mutations may want to speak with their medical teams about taking a PARP inhibitor such as t**alazoparib (Talzenna)** or **olaparib (Lynparza)**, which are approved for HER2- MBC patients with *BRCA* mutations in the US and elsewhere. Additional information is available in the chapter entitled, *"Approved Therapies for Patients with BRCA Mutations."*

- **Datopotamab deruxtecan-dlnk (Datroway).** In January 2025, the FDA approved **datopotamab deruxtecan-dlnk (Datroway)** as second- or later-line treatment for metastatic HR+, HER2- or HER2-low breast cancer after endocrine therapy and chemotherapy. **Datopotamab deruxtecan-dlnk (Datroway)** is given by IV once every 3 weeks. Approval was based on the Phase 3 TROPION-Breast01 (NCT05104866) clinical trial, which enrolled 732 patients. Median progression-free survival was 6.9 months in the **datopotamab deruxtecan-dlnk (Datroway)** arm and 4.9 months in the chemotherapy arm, a difference that was significant. There was no difference in median overall survival (18.6 months with **datopotamab deruxtecan-dlnk (Datroway)** and 18.3 months with chemotherapy). Side effects experienced by ≥20% of patients included mouth sores, nausea, vomiting, fatigue, decreased white blood cells, decreased calcium, hair loss, decreased hemoglobin, constipation, dry eye, increased liver enzymes, eye inflammation, and increased alkaline phosphatase. From: ***https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-datopotamab-deruxtecan-dlnk-unresectable-or-metastatic-hr-positive-her2-negative-breast#:~:text=On%20January%2017%2C%202025%2C%20the,epidermal%20growth%20factor%20receptor%202%20***
- **Fam-trastuzumab deruxtecan-nxki (T-DXd; Enhertu):** This HER2-directed antibody-drug conjugate (ADC) was FDA

approved in Aug. 2022 for hormone receptor-negative, HER2- patients whose HER2 expression is considered to be "HER2-low," (IHC 1+, or IHC 2+ with negative results on in situ hybridization) or "ultralow" (IHC 0 with membrane staining) and who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy.

- **Sacituzumab govitecan (Trodelvy)** was recently approved by the FDA (February 2023) as third- or later-line therapy for HR+, HER2- MBC. Sacituzumab govitecan (Trodelvy), which is administered intravenously, consists of the chemotherapy drug irinotecan linked with an antibody targeted against TROP-2, a cell-surface protein. Approval was based upon the TROPiCS02 trial (NCT03901339), which enrolled 543 HR+/HER2− MBC patients who had progressed after at least 1 endocrine therapy, taxane, and CDK4/6 inhibitor in any setting and who had received between 2 and 4 lines of chemotherapy for metastatic disease. Patients were randomly assigned to sacituzumab govitecan (Trodelvy) (272 patients) or to a treatment of physician's choice [(capecitabine (Xeloda), vinorelbine (Navelbine), gemcitabine (Gemzar), or eribulin (Halaven)]; 271 patients). At 12 months, progression-free survival (PFS) rates were 21% and 7%, respectively. Median PFS with sacituzumab govitecan (Trodelvy) was 5.5 months and with chemotherapy was 4 months. Median overall survival was 14.4 vs 11.2 months, respectively. The PFS benefit with sacituzumab govitecan (Trodelvy) was consistent across predefined subgroups, including patients with ≥3 prior chemotherapy regimens, those with visceral metastases, and patients aged 65 years and older. From: ***https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-sacituzumab-govitecan-hziy-hr-positive-breast-cancer***
- If a US patient's cancer has microsatellite instability-high (MSI-H), mismatch repair deficient (dMMR) characteristics (which are very rare), or is tumor mutational burden-high (TMB-H), and if the patient has progressed on prior therapy and has no satisfactory treatment options, pembrolizumab (**Keytruda)** (a PD-1 inhibitor), is an FDA-approved option. This therapy was also approved for patients with unresectable or metastatic TMB-H solid tumors. **Dostarlimab-gxly (Jemperli)** has also been FDA approved for the treatment of adult patients with dMMR recurrent or advanced solid tumors, as determined by an FDA-approved test,

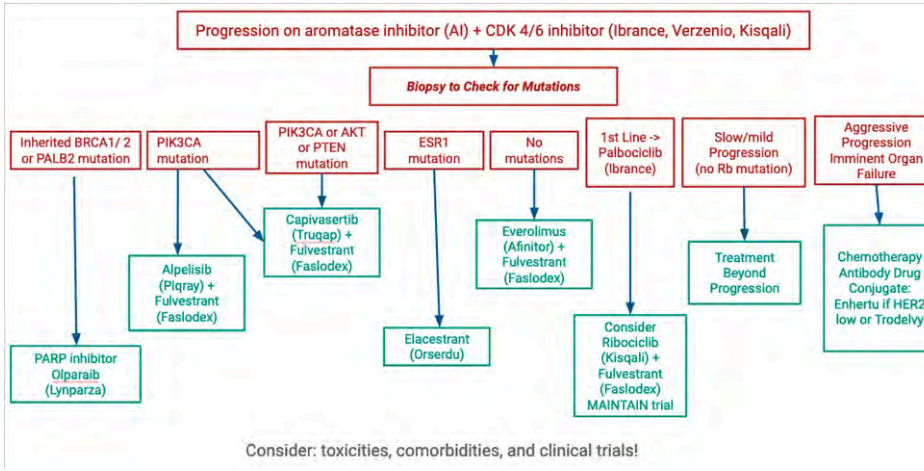
who have progressed on or following previous treatment and who have no satisfactory alternative options.

- Similar to the above, if a US patient's cancer has a neurotrophic receptor tyrosine kinase (*NTRK*) gene fusion without a known acquired resistance mutation, and if there has been progression on prior therapy with no satisfactory treatment options, **larotrectinib (Vitrakvi)** and **entrectinib (Rozlytrek)** - oral tyrosine kinase inhibitors that acts as an "on" or "off" switch in many cellular functions – are FDA-approved options. *NTRK* fusions are extremely rare, occurring in only about 0.5–1% of common cancers. Additional information is contained in the chapter, *"Approved Therapies Based Upon Tumor Characteristics."*

Patients are urged to discuss the various treatment options with their medical teams and verify insurance coverage, since it is possible that some of the drug regimens listed below may not be fully covered by insurance, or they may be expensive.

Readers are highly encouraged to review the sections in this Guide about Hormonal Therapy and Targeted Therapy for further information.

The below flowchart may help you understand treatment selection after progression:



HORMONAL (ENDOCRINE) AND TARGETED THERAPY SEQUENCE FOR PREMENOPAUSAL PATIENTS IN THE US

The sequence of providing hormonal (endocrine) therapy for premenopausal patients will vary, as much of it depends upon what - if any - hormonal therapy drugs the patient has previously taken in the adjuvant and/or metastatic setting, and how recently they were administered. The sequence will also depend upon the country in which the patient resides, with the US listed immediately below. (Therapies for premenopausal MBC patients in Canada, Europe, and Australia are provided in subsequent sections).

First-Line Hormonal and Targeted Treatment Options for Premenopausal Patients in the US:

- **The combination of a CDK4/6 inhibitor such as palbociclib (Ibrance), ribociclib (Kisqali), or abemaciclib (Verzenio) with either an aromatase inhibitor (letrozole (Femara), anastrozole (Arimidex), or exemestane (Aromasin), or with fulvestrant (Faslodex) is the current standard-of-care as initial treatment, along with an LHRH agonist.**

- **An aromatase inhibitor alone (but with an LHRH agonist**).

- **Fulvestrant (Faslodex) with either letrozole (Femara) or anastrozole (Arimidex) (with an LHRH agonist).**

- **Fulvestrant (Faslodex) alone (but with an LHRH agonist).**

- **Tamoxifen (Nolvadex) or toremifene (Fareston) with an LHRH agonist is also a first-line therapeutic option**.

After progression if the patient still has her ovaries, **an oophorectomy** may be appropriate because it will remove a key source of estrogen from being produced by the body. After an oophorectomy, the patient is considered postmenopausal and would follow the hormonal therapy guidelines for postmenopausal

patients. For patients deciding against an oophorectomy, the therapies below can be considered.

Second-Line Hormonal and Targeted Treatment Options for Premenopausal Patients in the US Depend Upon What Endocrine Therapy Regimen the Patient has Previously Taken:

- **Possibly any of the above therapies.**

- **Alpelisib (Piqray)** in combination with fulvestrant (Faslodex) and an LHRH agonist if the cancer has a *PI3K* mutation and you have progressed on at least one endocrine-based therapy *(if you were premenopausal when diagnosed, you must be deemed postmenopausal to be eligible for alpelisib (Piqray)).*

- **Talazoparib (Talzenna) or olaparib (Lynparza)** if you have a germline (inherited) *BRCA1* or *BRCA2* mutation and you have received at least one prior chemotherapy.

- **Fam-trastuzumab-deruxtecan-nxk (T-DXd; Enhertu)** if your cancer's HER2 expression is either +1, or +2 with negative results on in situ hybridization and you have received at least one prior chemotherapy.

- **With an LHRH agonist, everolimus (Afinitor) can be taken in combination with either exemestane (Aromasin), fulvestrant (Faslodex), or tamoxifen (Nolvadex)**, and one study showed that it conferred a median progression-free survival of 5.9 months for patients who had previously taken a CDK4/6 inhibitor.

Later-Line Hormonal and Targeted Treatment Options for Premenopausal Patients in the US:

Patients may want to reconsider having an oophorectomy and possibly taking different endocrine-based therapy. Chemotherapy is usually prescribed after 2 to 3 lines of endocrine-based therapies (and/or the targeted therapies above) have stopped working. A clinical trial may also be a consideration. Once the cancer has regressed or stabilized, it may be possible to go back on a previous therapy if sufficient time has elapsed and if the initial response to the therapy had been favorable.

HORMONAL (ENDOCRINE) AND TARGETED THERAPY SEQUENCE FOR POSTMENOPAUSAL PATIENTS IN THE US

The sequence of providing hormonal (endocrine) therapy for postmenopausal patients will vary, since much of it depends upon what - if any - hormonal therapy drugs the patient has previously taken in the adjuvant and/or metastatic setting, and how recently they were administered. The sequence will also depend upon the country in which the patient resides, with the US listed immediately below. (Therapies for postmenopausal MBC patients in Canada, Europe, and Australia are provided in subsequent sections).

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

- The combination of a CDK4/6 inhibitor such as palbociclib (Ibrance), ribociclib (Kisqali), or abemaciclib (Verzenio) with either an aromatase inhibitor (letrozole (Femara), anastrozole (Arimidex), or exemestane (Aromasin), or with Faslodex (fulvestrant (Faslodex) **is the current standard-of-care as initial treatment.**

- **An aromatase inhibitor** alone

- **Fulvestrant (Faslodex) with either letrozole (Femara) or anastrozole (Arimidex)**

- **Fulvestrant (Faslodex)** alone

- **Tamoxifen (Nolvadex) or toremifene (Fareston)** alone *(rarely used as a first-line therapy).*

FDA-Approved Second-Line Hormonal and Targeted Treatment Options for Postmenopausal Patients in the US (depending upon prior treatment):

- **Possibly any of the above therapies.**

- **Alpelisib (Piqray) in combination with fulvestrant (Faslodex) and an LHRH agonist if the cancer has a *PI3K* mutation** and you have progressed on at least one endocrine-based therapy *(if you were initially premenopausal when diagnosed, you must be deemed postmenopausal to be eligible for alpelisib (Piqray))*.

- **Talazoparib (Talzenna) or olaparib (Lynparza) if you have a germline (inherited) *BRCA1* or *BRCA2* mutation** and you have received at least one prior chemotherapy.

- **Fam-trastuzumab-deruxtecan-nxk (T-DXd; Enhertu) if your cancer's HER2 expression is either +1, or +2 with negative results** on in situ hybridization and you have received at least one prior chemotherapy.

- **Everolimus (Afinitor) can be taken in combination with either exemestane (Aromasin), fulvestrant (Faslodex), or tamoxifen (Nolvadex),** and one study showed that it conferred a median progression-free survival of 5.9 months for patients who had previously taken a CDK4/6 inhibitor.

FDA-Approved Third-Line and Above Hormonal and Targeted Treatment Options for Postmenopausal Patients in the US (depending upon prior treatment):

- **Possibly any of the above therapies** (although not all options are widely used in a third- or later-line setting).

- **Abemaciclib (Verzenio) alone** *(after disease progression on endocrine therapy and prior chemotherapy for MBC)*.

- **Ethinyl estradiol, megestrol acetate (Megace), or fluoxymesterone (Halotestin).**

Chemotherapy is usually prescribed after 2 to 3 lines of endocrine-based therapies (and/or the targeted therapies above) have stopped working. A clinical trial may also be a consideration. Once the cancer has regressed or stabilized, it may be possible to go back on a previous therapy if sufficient time has elapsed and if the initial response to the therapy had been favorable.

HORMONAL AND TARGETED THERAPY SEQUENCE FOR PREMENOPAUSAL PATIENTS IN CANADA

(Although the author has endeavored to procure and provide treatment information for Canadian MBC patients, the list below may nevertheless be incomplete, and patients are urged to fully review and discuss treatment options with their medical teams).

Ovarian ablation or ovarian suppression should be combined with an aromatase inhibitor (letrozole (Femara), anastrozole (Arimidex), or exemestane (Aromasin)). Premenopausal women who do not want to have ovarian ablation or ovarian suppression may be offered tamoxifen (Nolvadex) alone.

HORMONAL AND TARGETED THERAPY SEQUENCE FOR POSTMENOPAUSAL PATIENTS IN CANADA

Hormonal and Targeted Treatment Options for Hormone Receptor-Positive, HER2- Patients in Canada (depending upon what, if any, recent treatments the patient may have had in the adjuvant setting):

- **Letrozole (Femara)** alone, or with a CDK4/6 inhibitor (**palbociclib (Ibrance), ribociclib (Kisqali), or abemaciclib (Verzenio**)
- **Anastrozole (Arimidex)** alone, or with **palbociclib (Ibrance)**
- **Exemestane (Aromasin)** alone, or with **palbociclib (Ibrance)**
- **Fulvestrant (Faslodex)** alone, or with **palbociclib (Ibrance)**
- **Tamoxifen (Nolvadex)** alone

* Canadian patients may want to consult with their physicians about abemaciclib (Verzenio) in combination with other hormonal therapies as possible first-line treatment based upon the statement made in 2019 that, “Verzenio is used… in combination with endocrine therapies that are already approved in Canada.” **From:**

https://www.biospace.com/article/releases/health-canada-approves-new-drug-to-treat-metastatic-breast-cancer-through-international-and-domestic-joint-reviews/

Later Line Treatments for Hormone Receptor-Positive, HER2- Canadian Patients:

- **Everolimus (Afinitor) in combination with exemestane (Aromasin)** (approved by Health Canada for after recurrence or progression following treatment with letrozole **(Femara)** or anastrozole (Arimidex))
- **Abemaciclib (Verzenio)** alone

The author was unable to locate further information about additional approved later line hormonal therapies for Canadian patients, and the above information has been gleaned **From:** ***https://cbcn.ca/en/listing-directory/drug-navigation-tool/palbociclib-fulvestrant*** and ***https://www.newswire.ca/news-releases/health-canada-approves-prafinitor-in-advanced-breast-cancer-for-women-battling-this-disease-511843901.html*** and ***https://www.biospace.com/article/releases/health-canada-approves-new-drug-to-treat-metastatic-breast-cancer-through-international-and-domestic-joint-reviews/***

GUIDELINES FOR HORMONE RECEPTOR-POSITIVE, HER2- MBC PATIENTS IN EUROPE - EXCEPT FOR COUNTRIES GOVERNED BY NICE

The European Society for Medical Oncology (ESMO) provides guidelines for treatment of people with MBC. The patient version can be found here: https://www.esmo.org/living-guidelines/esmo-metastatic-breast-cancer-living-guideline.

European (except for NICE) Guidelines state: *"Patients with ER-positive, HER2- metastatic breast cancer should receive endocrine therapy with an aromatase inhibitor (Letrozole, Arimidex, or Aromasin), or Faslodex plus a CDK4/6 inhibitor (Ibrance, Kisqali, or Verzenio) in the frontline setting. In patients for whom organ failure is imminent, chemotherapy followed by maintenance or next-line endocrine therapy plus a CDK4/6 inhibitor should be considered.*

Upon progression, patients without a risk of organ failure are eligible for Faslodex plus a CDK4/6 inhibitor if not previously used, Afinitor/Aromasin or Afinitor/Faslodex, Faslodex/Piqray if PIK3CA mutated, or a PARP inhibitor (Lynparza or Talzenna) if BRCA/PALB2 mutated. Chemotherapy should be given upon progression after several lines of endocrine therapy with or without targeted therapies." **From:** ***https://www.onclive.com/view/esmo-guidelines-recommend-personalized-treatment-and-multidisciplinary-decision-making-in-breast-cancer?fbclid=IwAR1g8ETQnQSVRfyoptCD853vdBIX8FgtXvKKT_gl7GAkQYnGkwatoeQyjQU***

<Author's note: Premenopausal patients would normally also be given a medication for ovarian suppression.>

SEQUENCE OF THERAPIES FOR HORMONE RECEPTOR-POSITIVE, HER2-MBC PATIENTS GOVERNED BY NICE GUIDELINES

(Although the author has endeavored to procure and provide treatment information for European MBC patients governed by NICE guidelines, the list below may nevertheless be incomplete, and patients are urged to fully review and discuss treatment options with their medical teams).

FOR PREMENOPAUSAL MBC PATIENTS GOVERNED BY NICE GUIDELINES:

- **Tamoxifen (Nolvadex) and ovarian suppression** should be used as first-line treatment if the premenopausal patient was not previously treated with tamoxifen (Nolvadex).
- For patients who had been pre-treated with tamoxifen (Nolvadex), **ovarian suppression** should be used as first-line treatment.

Premenopausal patients should consult with their doctors about the NICE guidelines below for postmenopausal patients, as they may likely apply to premenopausal patients with ovarian suppression.

FOR POSTMENOPAUSAL MBC PATIENTS GOVERNED BY NICE GUIDELINES:

First-Line Hormonal and Targeted Treatment Options as per NICE Guidelines for Postmenopausal Patients:

- An aromatase inhibitor **(letrozole (Femara), anastrozole (Arimidex), or exemestane (Aromasin))** alone, or with a CDK4/6 inhibitor **(palbociclib (Ibrance), ribociclib (Kisqali), or abemaciclib (Verzenio))**
- **Tamoxifen (Nolvadex)** (for men with MBC)

Second-Line Hormonal and Targeted Treatment Options as per NICE Guidelines for Postmenopausal Patients:

- An aromatase inhibitor **(letrozole (Femara), anastrozole (Arimidex), or exemestane (Aromasin))** alone if the patient had previously received tamoxifen or chemotherapy
- **Everolimus (Afinitor) and exemestane (Aromasin)** (for women without symptomatic visceral disease that has progressed after a non-steroidal aromatase inhibitor [**letrozole (Femara)** or **anastrozole (Arimidex)**])
- **Abemaciclib (Verzenio) and fulvestrant (Faslodex)** (for women without symptomatic visceral disease that has progressed after a non-steroidal aromatase inhibitor [letrozole (Femara) or anastrozole (Arimidex)])
- **Palbociclib (Ibrance) and fulvestrant (Faslodex)** after prior endocrine therapy
- **Ribociclib (Kisqali) and fulvestrant (Faslodex)** after prior endocrine therapy
- **If the cancer has a *PIK3CA* mutation,** alpelisib (**Piqray) in combination with fulvestrant (Faslodex)** was approved in July 2022.

For MBC patients in Scotland: The Scottish Medicines Consortium (SMC) indicated that **palbociclib (Ibrance) or ribociclib (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.

THERAPIES FOR HORMONE RECEPTOR-POSITIVE, HER2- MBC PATIENTS IN AUSTRALIA

The author offers apologies because it was not possible to locate viable websites regarding specific hormonal and targeted therapy

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

That said, MBC patients in Australia have reported that **letrozole (Femara), anastrozole (Arimidex), exemestane (Aromasin), and tamoxifen (Nolvadex)** (as well as a similar drug called **Toremifene (Fareston)**) may be used alone in the first or second line setting. Additionally, after failure of **letrozole (Femara)** or **anastrozole (Arimidex), everolimus (Afinitor)** may be paired with **exemestane (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. In April 2019, **abemaciclib (Verzenio)** (a CDK4/6 inhibitor) was approved for use in Australia. It is assumed that **abemaciclib (Verzenio)** can be paired with an approved endocrine therapy in the first-line setting, or as a monotherapy after an endocrine therapy and a chemotherapy have failed. This assumption is based on the fact that Australia's Therapeutic Goods Administration (TGA) and Health Canada have jointly approved **abemaciclib (Verzenio)** for the treatment of metastatic breast cancer, and Health Canada has stipulated that **abemaciclib (Verzenio)** can be paired with an approved endocrine therapy in the first-line setting, or as a monotherapy after an endocrine therapy and a chemotherapy have failed as per: ***https://www.biospace.com/article/releases/health-canada-approves-new-drug-to-treat-metastatic-breast-cancer-through-international-and-domestic-joint-reviews/***

Interestingly, although one website indicated that **fulvestrant (Faslodex)** is an option for Australian patients who have received prior treatment with **tamoxifen (Nolvadex), fulvestrant (Faslodex))** was not listed on Australia's PBS as of January 2020. For those wanting further information, a PBS search by drug name is available at: ***http://www.pbs.gov.au/browse/medicine-listing?initi***

Guidelines for patients living in resource-constrained countries are provided by the American Society of Clinical Oncology (ASCO): ***https://ascopubs.org/doi/10.1200/GO.23.00285***

OTHER CONSIDERATIONS REGARDING HORMONAL AND TARGETED THERAPIES, INCLUDING RESISTANCE

Rising *ESR1* mutations while taking palbociclib (Ibrance) and an aromatase inhibitor: As per the Phase 3 PADA-1 trial, patients with rising *ESR1* mutations who were taking **palbociclib (Ibrance)** in combination with an aromatase inhibitor **(letrozole (Femara), anastrozole (Arimidex), or exemestane (Aromasin))** in the first-line setting who switched to **fulvestrant (Faslodex) plus palbociclib (Ibrance)** before disease progression had a doubling of progression-free survival (PFS) compared with patients who were not switched. At a median follow-up of 26 months, the median PFS was 11.9 months in patients who switched to **fulvestrant (Faslodex)** vs. 5.7 months for patients who did not switch. Patients who remained on **palbociclib (Ibrance)** with an aromatase inhibitor who subsequently developed progression and switched to **fulvestrant (Faslodex)** had a median PFS of 3.5 months, so there appears to be a benefit of switching from an aromatase inhibitor to **fulvestrant (Faslodex)** prior to progression when *ESR1* mutations arise.

As an aside, *ESR1* mutations can be detected in the blood by cell-free circulating DNA analysis. These mutations are detected in less than 5% of patients at metastatic relapse but are identified in 30-40% of patients at progression following first-line aromatase inhibitor-based therapy. **From:**
https://www.targetedonc.com/view/pfs-doubles-with-fulvestrant-palbociclib-following-ai-palbociclib-in-hr-positive-her2-negative-mbc

Effect of proton pump inhibitors on palbociclib (Ibrance): Proton pump inhibitors (PPIs) are frequently prescribed for the management of anticancer drug-related gastrointestinal (GI) symptoms. In a retrospective observation study of 112 patients who took the CDK4/6 inhibitor **palbociclib (Ibrance)** with endocrine therapy, it was noted that patients taking PPIs had a shorter progression-free survival than those who were not taking PPIs (14.0 versus 37.9 months). However, according to Pfizer's website, "Drug interaction was observed when **IBRANCE** capsules were coadministered with proton pump inhibitors (PPIs) under fasted conditions but was limited when IBRANCE capsules were coadministered with PPIs under fed conditions. Food

intake with administration of **IBRANCE** capsules reduced the variability of palbociclib exposure. Coadministration of IBRANCE tablets with PPIs under fasted conditions had no effect on palbociclib absorption." Readers taking **palbociclib (Ibrance)** and PPIs are encouraged to discuss the coadministration of **palbociclib (Ibrance)** and PPIs with their medical teams and not make any changes to their treatment unless professional medical advice has been obtained. (NOTE: Several lines of evidence suggest no impact of PPIs on the bioavailability of **ribociclib (Kisqali)**. A study of Japanese patients who received **abemaciclib (Verzenio) or palbociclib (Ibrance)** showed no difference in progression-free survival or overall survival between those who took a PPI and those who did not. **From:** ***https://www.esmoopen.com/article/S2059-7029(21)00192-7/fulltext and https://www.practiceupdate.com/C/162751/56?elsca1=emc_enews_topic-alert***

Taking palbociclib (Verzenio) after prior failure of a CDK4/6 inhibitor: Although **palbociclib (Ibrance), ribociclib (Kisqali), and abemaciclib (Verzenio)** are CDK4/6 inhibitors, **abemaciclib (Verzenio)** works somewhat differently. In an effort to determine whether **abemaciclib (Verzenio)** might be effective in patients previously treated with **palbociclib (Ibrance)**, the Moffitt Cancer Center presented a Poster at SABCS 2019 regarding study results of 28 heavily pre-treated hormone receptor-positive, HER2- MBC patients who had previously progressed on **palbociclib (Ibrance)** with endocrine therapy and had subsequently taken **abemaciclib (Verzenio)** (either as monotherapy or in combination with endocrine therapy). Of these patients, 23 (82.1%) had visceral involvement and 9 (32.1%) had brain metastases. These patients had received a mean of 5.4 prior lines of therapy, including chemotherapy. A total of seven (25%) patients had a durable response to **abemaciclib (Verzenio)**. Of those patients, 3 had a longer progression-free survival (PFS) compared with their prior PFS on **palbociclib (Ibrance)**. Of the patients with a durable response, 5 had available genomic profiling: 2 (28.5%) patients had an *ESR1* mutation, and 3 (42.8%) had *PIK3CA* mutations. It was concluded that age, duration of previous palbociclib (Ibrance)-based therapy, number of prior therapies, presence of visceral or brain metastatic disease, number of mutations, and presence of *ESR1* or *PIK3CA* mutations did not affect PFS on **abemaciclib (Verzenio)**-based therapy.

From Feb. 2015 to Jan. 2019, a somewhat larger study evaluated clinical outcomes in patients with HR+/HER2- MBC who received

abemaciclib (Verzenio) after progressing on either **palbociclib (Ibrance)** or **ribociclib (Kisqali)** in combination with endocrine therapy. Although 20 (34%) of the patients on **abemaciclib (Verzenio)** had disease progression in less than 3 months, 21 patients (36%) had a treatment response duration exceeding 6 months - including 10 patients who remained on treatment at interim analysis (range 181-413 days). The median progression-free survival on **abemaciclib (Verzenio)** following a prior CDK4/6 inhibitor was 5.8 months. In another study reported at SABCS 2023 (PO1-13-02), analysis of circulating tumor DNA in patients with HR+ HER2- MBC treated with abemaciclib (Verzenio) in any line of therapy showed new mutations in *PIK3CA*, *TP53*, *ESR1*, *FGF3/4/19*, and *RB1* acquired after abemaciclib (Verzenio) treatment. **From:** ***https://meetinglibrary.asco.org/record/175766/abstract***

Potential impact of being on a CDK4/6 inhibitor before moving on to everolimus (Afinitor):
A small study examined the medical records of 33 patients who underwent therapy with **everolimus (Afinitor)** and **exemestane (Aromasin)** (A/A). 17 of the patients had prior CDK4/6 inhibitor therapy combined with endocrine therapy, and 16 had taken either **letrozole (Femara)** or **anastrozole (Arimidex)** alone. In patients who had previously received a CDK4/6 inhibitor, the progression-free survival was 5.7 months vs. 4.7 months in patients who had taken **letrozole (Femara) or anastrozole (Arimidex)** alone. The median overall survival of patients who'd had a prior CDK4/6 inhibitor was 17.8 months vs. 11.4 months for those who had only taken **letrozole (Femara) or anastrozole (Arimidex)**. The study concluded that A/A was effective for patients who had previously received CDK4/6 inhibitor therapy and for those who had received prior therapy with an aromatase inhibitor alone.

Another study called TRINITI-1 evaluated triplet therapy with **ribociclib (Kisqali)**, **everolimus (Afinitor)**, and **exemestane (Aromasin)** among 95 men and postmenopausal women with advanced hormone receptor-positive, HER2- breast cancer who received previous CDK4/6 inhibitor therapy and up to three lines of prior treatment. The clinical benefit rate at 6 months was 41.1% (which was four times the minimum threshold for the study), the disease control rate was 61.1%, and the overall response rate was 8.4%. The median progression-free survival was 5.7 months. **From**: ***https://www.healio.com/hematology-oncology/breast-cancer/news/online/%7Be782030f-fd3f-47d2-9735-ad3c2d4cd2e6%7D/triplet-therapy-***

confers-benefit-among-certain-patients-with-advanced-breast-cancer?page=2

Potential impact of being on everolimus (Afinitor) before moving on to palbociclib (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 **palbociclib (Ibrance).** In the small population in the study (23 patients), the median progression-free survival was 2.9 months for patients who had previously taken **everolimus (Afinitor)** and then moved on to a **palbociclib (Ibrance)** regimen, versus 9.5 months for patients on **palbociclib (Ibrance)** who had not previously been on **everolimus (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 **everolimus (Afinitor)** before palbociclib (Ibrance) (or other CDK4/6 inhibitors) is definitively associated with a low response and clinical benefit rate. **From[25]:** ***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 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.*

Aromatase inhibitors (AIs) may cause a loss of bone density, which leads to higher rates of osteoporosis and bone fractures compared to **tamoxifen (Nolvadex)**. 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 **denosumab (Xgeva)** to help preserve bone density. In turn, bisphosphonates and **denosumab (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 may occur. If possible, patients should have a dental exam (and inform their dentist about their drug plan)

before using a bisphosphonate or **denosumab (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[26, PMID:16030366]:** ***http://ww5.komen.org/BreastCancer/AromataseInhibitors.html*** and ***http://www.medscape.com/viewarticle/509074_7***

Although a patient's HER2 status may officially be negative as per their pathology report, in some cases HER2-directed treatment may be viable. For example, the drug fam-trastuzumab deruxtecan-nxki (T-DXd; Enhertu) has been approved for patients with HER2-low expression (IHC value +1 or +2 and negative for *HER2* gene amplification by in situ hybridization). Additional information about **fam-trastuzumab deruxtecan-nxki (T-DXd; Enhertu)** is located under "*Research and Potential Therapies for HER2- (or Low) MBC."*

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 that specifically target these factors. Additional information about ARs and FGFR1/11q is located in the section entitled *"Research and Potentially Helpful Therapies."*

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 it 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 of - and Biomarkers for - Hormonal Therapy Resistance:

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 or in a clinical trial, or explore other therapies listed in this Guide. 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 chemotherapy or in a clinical trial, or explore other therapies listed in this Guide.

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 a tumor biopsy, or a blood test designed to analyze circulating tumor DNA (ctDNA)). Fulvestrant (Faslodex) is the preferred endocrine treatment over aromatase inhibitors for patients with *ESR1* mutations.
In January 2023, the FDA approved elacestrant (Orserdu), the first oral SERD, as second-line treatment for postmenopausal women or men with ER+, HER2- MBC with a mutation in *ESR1*. This mutation can be detected with an FDA-approved companion diagnostic test. From: ***https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-elacestrant-er-positive-her2-negative-esr1-mutated-advanced-or-metastatic-breast-cancer***

Similar to *ESR1* mutations, ***HER2*** **(ERBB2) mutations** appear to be associated with resistance to endocrine 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- in terms of treatment options.

Tumors with amplification of *FGFR1* or loss of *PTEN* or *Rb1* may be predictive for resistance to CDK4/6 inhibitors. **From:** ***https://www.targetedonc.com/view/emerging-biomarkers-inform-therapy-choice-in-hr-breast-cancer***

In November 2023, the FDA approved capivasertib (Truqap) plus fulvestrant (Faslodex) as second-line treatment for HR+, HER2- MBC with alterations in the genes PIK3CA, AKT1, and/or PTEN. These alterations can be detected with an FDA-approved companion diagnostic test. From: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-capivasertib-fulvestrant-breast-cancer

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:** ***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 estrogen receptors (ERs), 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. Progesterone receptors (PRs), on the other hand, arelost 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[27, PMID:PMC3656649]:**
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3656649/

Tamoxifen (Novalidex) Resistance: For patients whose doctors recommend that they start taking **tamoxifen (Nolvadex)**, and for patients who are currently taking **tamoxifen (Nolvadex)** and not responding, a "CYP2D6" test may be an option. This is because some people simply will not respond to **tamoxifen (Nolvadex)** 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 **toremifene (Fareston),** which is a selective estrogen receptor modulator (SERM) similar to **tamoxifen (Nolvadex)**, may be an alternative for postmenopausal (not premenopausal) women. **From:**
https://pubmed.ncbi.nlm.nih.gov/29978573/#:~:text=Toremifene%20(TOR)%20is%20a%20valid,%25%2C%20p%20=%200.188)

In closing, below are some tips when taking fulvestrant (Faslodex) :
Fulvestrant (Faslodex) injections are administered intramuscularly in the buttocks and can be quite uncomfortable during and after the shots, which is due in part to the thickness of the liquid. These suggestions should help to minimize discomfort:

- Consider taking an over-the-counter pain relief tablet an hour or two before the injection.
- Warm the syringes under your armpits for several minutes until the liquid reaches body temperature, which makes the shots easier to administer.
- Ask the nurse to gently massage the injection sites before the injections.
- Have the nurse put numbing spray on the area before injecting the drug.
- Traditionally, nurses have been trained to inject into the dorsogluteal site; however, the ventrogluteal site is evolving as a safer intramuscular injection site. **From:** ***https://voice.ons.org/conferences/best-practices-for-im-injection-of-fulvestrant***
- Ensure that the nurse will use the "Z-track" method for the injections to prevent leakage of the liquid into the subcutaneous tissue. Z-track instructions are located at: ***https://www.healthline.com/health/z-track-injection#how-to***
- Make sure the nurse will inject the liquid slowly (1 – 2 minutes per injection).
- 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).

- After the injection, apply 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.

For additional information, suggested sections include:

Personalized Medicine
Hormonal Therapy
Chemotherapy
Targeted Therapy
Research and Potentially Helpful Therapies

8. HER2+/Hormone Receptor-Negative MBC & Related Therapies

The National Comprehensive Cancer Network (NCCN) provides guidelines for treatment of people with MBC. The patient version can be found here: ***https://www.nccn.org/patients/guidelines/content/PDF/stage_iv_breast-patient.pdf***. More information is available in the professional guidelines: (***https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf***).
You can create a free account to view the professional guidelines. The information provided below is current as of 2023. Please see the above guidelines for the most recent updates.
In addition, the American Society of Clinical Oncology (ASCO) also provides guidelines.

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+).

HER2+ breast cancers tend to grow faster and are more likely to spread and come back compared to HER2- breast cancers. But there are currently many medicines specifically targeting HER2+ 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 subtypes.

Some breast cancers that are initially HER2+ can become HER2- 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.

TYPES OF DRUGS USED IN HER2 THERAPY:

- **Monoclonal Antibodies:** Antibodies are an integral part of the body's immune system. Normally the body creates antibodies in response to an "antigen" (a germ that has entered the body, or a specific protein). Antigens are molecules capable of stimulating an immune response, and each antigen has distinct surface features that result in specific responses. Antibodies attach to the antigen in order to mark it for destruction by the immune system. When given to a patient, specific antibodies will attach to matching antigens in much the same way that a key fits a lock. Monoclonal antibodies are laboratory-produced molecules that serve as substitute antibodies that can restore, enhance, or mimic the immune system's attack on cancer cells. They are designed to bind to antigens that are generally more numerous on the surface of cancer cells than healthy cells.

- **Antibody Drug Conjugates (ADCs):** ADCs comprise an antibody that recognizes a target on the cancer cell surface linked to a chemotherapy payload that is released when the antibody binds to that target. In an ideal world, these cell-surface targets would only be expressed on cancer cells, but there can be lower expression of them on normal cells, contributing to side effects due to interactions with normal cells. The goal of ADCs is to deliver chemo where it's needed and not everywhere in the body. Because ADCs are more specific than chemotherapy, they tend to be better tolerated by patients. However, the chemotherapy molecule can "fall off" the ADC and be released into the bloodstream, leading to side effects similar to traditional chemotherapies. Researchers are working to improve ADCs so that they release their chemotherapy payload only where needed. Additionally, some ADCs can cause antibody-specific and sometimes serious side effects such as lung damage (interstitial lung disease or pneumonitis). It's important to be aware of the side effects associated with specific ADCs (for

example fam-trastuzumab deruxtecan-nxki (T-DXd; Enhertu) versus sacituzumab govitecan (Trodelvy)), as they can differ significantly.

- **Tyrosine Kinase Inhibitors:** This class of drugs targets enzymes important for cell functions (called "tyrosine kinase" enzymes). Tyrosine kinase enzymes are responsible for the activation of proteins involved in many cellular functions. Since tyrosine kinases help to send growth signals in cells, blocking them stops the cell growing and dividing.

- **Chemotherapy ("chemo") drugs:** Cells within the body continually grow, divide, and die. Cancer cells tend to divide and form new cells more quickly than normal cells, making them more vulnerable to chemotherapy drugs. Chemotherapy drugs target cells at different phases of the process of forming new cells, called the "cell cycle." But because chemotherapy drugs can't distinguish between healthy cells and cancer cells, normal cells are damaged along with the cancer cells, causing side effects. Each time chemo is given, it means trying to find a balance between killing the cancer cells in order to cure or control the disease, and sparing the normal cells to lessen side effects.

- **Bone-directed Therapies:** Patients with **bone metastases** should receive a bone-directed therapy such as **denosumab (Xgeva or Prolia)**, which is given by injection**,** or **zoledronic acid (Zometa)**, which is administered by infusion, in addition to their cancer-directed therapy. These drugs help to prevent fractures and other cancer-related bone problems in adults with cancer that has spread to the bones.

Specific HER2+ breast cancer treatments

- **Trastuzumab (Herceptin),** which is administered intravenously, an FDA-approved biosimilar (as per the *Biosimilars* section), or the FDA-approved version called **"trastuzumab and hyaluronidase-oysk" (Herceptin Hylecta**), which is administered via a subcutaneous injection**.** These drugs are a type of

monoclonal antibody. Since **trastuzumab (Herceptin)** can cause congestive heart failure in some instances, all breast cancer patients who are candidates for treatment with **trastuzumab (Herceptin)** should undergo cardiac testing prior to therapy and thereafter be monitored for heart damage regardless of age. **From[33, PMID:27091709]:** ***http://www.eurekalert.org/pub_releases/2016-04/uhn-bcp041916.php***

- **Margetuximab (Margenza),** a monoclonal antibody that is administered intravenously.

- **Pertuzumab (Perjeta),** which is a type of monoclonal antibody that is administered intravenously. Because **pertuzumab (Perjeta)** binds to a different area of the HER2 protein than **trastuzumab (Herceptin)**, when **pertuzumab (Perjeta)** is combined with **trastuzumab (Herceptin)**, a more complete blockage of HER2 signaling occurs.

- **Phesgo** is an injectable combination of **trastuzumab (Herceptin), pertuzumab (Perjeta)**, and hyaluronidase-zzxf.

- **Trastuzumab emtansine (T-DM1; Kadcyla**). **Trastuzumab emtansine (T-DM1; Kadcyla)** is an antibody-drug conjugate (ADC) consisting of trastuzumab (mentioned above) linked to a cytotoxic (cancer-killing) agent called DM1. It is administered intravenously.

- **Neratinib (Nerlynx),** a tyrosine kinase inhibitor that is provided in tablet form.

- **Lapatinib (Tykerb),** a tyrosine kinase inhibitor which is administered in tablet form.

- **Fam-trastuzumab deruxtecan-nxki (T-DXd; Enhertu): Fam-trastuzumab deruxtecan-nxki (T-DXd; Enhertu)** is a HER2-targeting antibody-drug conjugate (ADC) that is administered intravenously.

- **Tucatinib (Tukysa): Tucatinib (Tukysa)** is a tyrosine kinase inhibitor that is provided in tablet form.

- **Taxanes** and other chemotherapy drugs.

NCCN GUIDELINES FOR HER2+, HORMONE RECEPTOR-NEGATIVE MBC PATIENTS IN THE US:

First-Line Treatment for HER2+, Hormone Receptor-Negative MBC Patients in the US:

A "triplet" combination of trastuzumab (Herceptin) or an approved biosimilar, or trastuzumab and hyaluronidase-oysk (Herceptin Hylecta), along with 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:** ***https://society.asco.org/sites/new-www.asco.org/files/content-files/practice-patients/documents/2024-Resource-Stratified-Summary-Recommendations.pdf***

HER2+ MBC patients throughout the world should be aware that treatment with a trastuzumab (Herceptin)-pertuzumab (Perjeta)-taxane combination has become the international standard of care for their disease. **From:** ***https://www.ncbi.nlm.nih.gov/pubmed/27250913***

Obtaining the above triplet as a first-line therapy was based upon findings in the CLEOPATRA study, which concluded that adding pertuzumab (Perjeta) to trastuzumab (Herceptin) and docetaxel (Taxotere) significantly improved median overall survival (OS). Patients in the study who received the triplet therapy had a median OS of 56.5 months versus 40.8 months for patients on trastuzumab (Herceptin) and docetaxel (Taxotere). This represents the best possible outcome for any MBC subtype on any type of therapy. **From:** ***https://www.targetedonc.com/news/novel-agents-may-challenge-standard-therapy-in-advanced-her2-breast-cancer***

It should be noted that the above first-line therapy may be effective even for patients who were pre-treated with trastuzumab (Herceptin). Furthermore, ASCO 2024 guidelines specifically state that patients who have finished trastuzumab

(Herceptin)-based adjuvant treatment more than 12 months before recurrence should follow first-line HER2-targeted therapy–based treatment recommendations.
From[32]: ***https://ascopubs.org/doi/pdf/10.1200/GO.23.00285***

That said, frontline treatment for HER2+ MBC patients was further researched in the Phase 2 PERNETTA trial, which randomized 210 previously untreated HER2+ MBC patients to receive either trastuzumab (Herceptin), pertuzumab (Perjeta), and chemotherapy ("Group 1") vs. trastuzumab (Herceptin) and pertuzumab (Perjeta) without chemotherapy ("Group 2"). (Patients whose disease progressed were given trastuzumab emtansine (T-DM1; Kadcyla) in the second-line setting). Results announced in July 2019 indicated that the overall survival (OS) was similar in both groups, although the progression-free survival (PFS) was much better in Group 1. For those patients in Group 1 who were HER2+, hormone receptor negative, the median PFS was 22.2 months vs. 8.8 months for similar patients in Group 2. However, the 2-year OS was nearly the same at 79.9% vs. 81.1%. The researchers therefore indicated that frontline trastuzumab (Herceptin) and pertuzumab (Perjeta) without chemotherapy may be considered for patients with low-to-intermediate tumor burden, especially since treatment toxicity is considerably reduced. **From:** ***https://www.targetedonc.com/publications/targeted-therapy-news/2019/july-2019/patients-with-mbc-have-reduced-toxicity-burden-with-dual-her2targeted-therapy-in-the-front-line***

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[30, PMID:24799465]:** ***http://www.ascopost.com/issues/june-25-2014/asco-clinical-practice-guideline-systemic-therapy-for-patients-with-advanced-her2-positive-breast-cancer/***

Note that **Phesgo** (an injectable combination of Herceptin, Perjeta, and hyaluronidase-zzxf) can be given with a taxane in the above setting.

Second-Line Treatment for HER2+, Hormone Receptor-Negative MBC Patients in the US:

Fam-trastuzumab deruxtecan-nxki (T-DXd; Enhertu), which has shown statistically significant improvement in progression-free survival (PFS) when compared with **trastuzumab emtansine (T-DM1; Kadcyla)** below as second-line treatment for HER2+ MBC, has been FDA-approved for HER2+ adult patients who have received a prior anti-HER2-based regimen either in the metastatic setting, or in the neoadjuvant or adjuvant setting and have developed disease recurrence during or within 6 months of completing therapy. The benefit was observed across all prespecified subgroups, including patients with brain metastases. As reported at ASCO 2024 (abstract #1025), mature data from DESTINY-Breast03 (NCT03529110) showed that median PFS was 29.0 months for fam-trastuzumab deruxtecan-nxki (T-DXd; Enhertu) and 7.2 months for trastuzumab emtansine (T-DM1; Kadcyla). Median overall survival was 52.6 months for fam-trastuzumab deruxtecan-nxki (T-DXd; Enhertu) and 42.7 months for trastuzumab emtansine (T-DM1; Kadcyla). **From: *https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-regular-approval-fam-trastuzumab-deruxtecan-nxki-breast-cancer***

Trastuzumab emtansine (T-DM1; Kadcyla) may 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 (Xeloda),** which provided an OS of 25.9 months. **(Trastuzumab emtansine (T-DM1; Kadcyla)** can also be a viable first-line therapy in patients for whom **trastuzumab (Herceptin), pertuzumab (Perjeta),** and a taxane might be too toxic). **From[34, PMID:26656517]:** ***http://www.jnccn.org/content/13/12/1475.full*** and ***https://www.kadcyla.com/***

Another second - (or later-) line therapy is the combination of the oral drug **tucatinib (Tukysa) with capecitabine (Xeloda) and trastuzumab (Herceptin) (or trastuzumab and hyaluronidase-oysk (Herceptin Hylecta)** or an approved biosimilar) for HER2+ MBC patients (including those with brain metastases) who received one or more HER2-directed therapies in the metastatic setting. Approval was based upon the results of the HER2CLIMB clinical trial in which 612 HER2+ MBC patients with an average of 4 prior treatment regimens (including patients with brain metastases - 40% of which were untreated, or treated and progressing), were randomized to receive either the triplet of

tucatinib (Tukysa) in combination with capecitabine (Xeloda) and trastuzumab (Herceptin), or the doublet of capecitabine (Xeloda) and trastuzumab (Herceptin). Progression-free survival (PFS) was 7.6 months for the triplet arm and 4.9 months for the doublet arm, and overall survival (OS) was 24.7 months vs. 19.2 months, respectively. Among patients with brain metastases, the PFS rate at 1 year was 24.9% in the triplet arm vs. 0% in the doublet arm, and the median PFS was 7.6 months vs. 5.4 months respectively; in this group, tucatinib (Tukysa) reduced the risk of death and the risk of the cancer growing by 40%. In people with visceral metastases (cancer that has spread to the lungs, liver, or other soft internal organs), tucatinib (Tukysa) reduced the risk of death and the risk of the cancer growing by 30%. The OSand PFS results were consistent across all prespecified subgroups based upon age, race, hormone receptor status, geographic location, and other factors. As reported at ASCO 2024 (abstract #1105), in patients with HER2-mutated MBC with or without brain metastases who had received at least one prior line of therapy, a basket trial (NCT04579380) showed that tucatinib (Tukysa) plus trastuzumab (Herceptin) provided a median PFS of 9.5 months and OS of 20.1 months, supporting further development of this combination for these patients. **From**: ***https://www.healio.com/hematology-oncology/breast-cancer/news/online/%7Be214fc90-55f9-43da-996c-adc16f7bae11%7D/fda-approves-tukysa-as-part-of-combination-therapy-for-breast-cancer*** and ***https://www.breastcancer.org/research-news/tukysa-plus-standard-care-continues-to-improve-survival-for-advanced-her2-positive***

Yet another option is **margetuximab (Margenza) in combination with chemotherapy** for HER2+ MBC patients who have received two or more prior anti-HER2 regimens, at least one of which was for metastatic disease. **Margetuximab's (Margenza's)** approval was based upon the SOPHIA trial in which patients were randomized to either **Margetuximab (Margenza)** plus chemotherapy or **trastuzumab (Herceptin)** plus chemotherapy. Median progression-free survival was 5.8 months for patients in the **margetuximab (Margenza)**/chemotherapy arm vs. 4.9 months for patients in the **trastuzumab (Herceptin)**/chemotherapy arm, a nominal difference of less than one month. At a median follow-up of 20.2 months, it was determined that the median overall survival was similar, at 21.6 months with **margetuximab (Margenza)** and 21.9 months with **trastuzumab (Herceptin)**. **From:**

https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-margetuximab-metastatic-her2-positive-breast-cancer and ***https://www.cancertherapyadvisor.com/home/cancer-topics/breast-cancer/breast-cancer-margetuximab-no-overall-survival-difference-trastuzumab/***

Third-(or Later-) Line Treatment for HER2+, Hormone Receptor-Negative MBC Patients in the US:

An option for third- (or later-) line therapy is the **combination of neratinib (Nerlynx) and capecitabine (Xeloda)**, which was FDA-approved in Feb. 2020 for HER2+ MBC patients who received two or more prior anti-HER2-based regimens in the metastatic setting. Approval was based upon results from the Phase 3 NALA trial, which showed that the combination of **neratinib (Nerlynx) and capecitabine (Xeloda)** reduced the risk of disease progression or death by 24% compared with **lapatinib (Tykerb)** plus **capecitabine (Xeloda)**. In the trial of 621 HER2+ MBC patients who were randomized to either **neratinib (Nerlynx)** + **capecitabine (Xeloda)** or **lapatinib (Tykerb)** + **capecitabine (Xeloda)**, the 12-month progression-free survival (PFS) rates were 29% for the **neratinib (Nerlynx)** combination vs. 15% for the **lapatinib (Tykerb)** combination, and the 24-month PFS rates were 12% and 3%, respectively. Moreover, the median overall survival was 21 months for patients on the **neratinib (Nerlynx)** combination vs. 18.7 months for patients on the **lapatinib (Tykerb)** combination. Of special interest was the fact that fewer patients required intervention for CNS metastases on the **neratinib (Nerlynx)** combination than on the **lapatinib (Tykerb)** combination. **From**: ***https://www.onclive.com/web-exclusives/fda-approves-neratinib-combo-for-her2-breast-cancer?utm_medium=email&utm_campaign=ONC+Breaking+News+2-26-20&utm_content=ONC+Breaking+News+2-26-20+CID_00e83ce7705b5e1d314f8139dcf0d0fb&utm_source=CM+ONCLIVE&utm_term=READ+MORE&fbclid=IwAR1ZLfCgiHnEqbrA4w0N83XRetyMwXZGixu3BfMrs1JO5CoiUIWiIkVbKJA***

As mentioned in the second-line setting above, the combination of the oral drug **tucatinib (Tukysa) with capecitabine (Xeloda) and trastuzumab (Herceptin) (or trastuzumab and hyaluronidase-oysk (Herceptin Hylecta)** or an approved biosimilar) is approved for HER2+ MBC patients (including those

with brain metastases) who received one or more HER2-directed therapies in the metastatic setting, and **margetuximab (Margenza)** has been approved in combination with chemotherapy for HER2+ MBC patients who have received two or more prior anti-HER2 regimens, at least one of which was for metastatic disease.

Additional Later-Line Treatment Options for HER2+, Hormone Receptor-Negative MBC Patients in the US:

- If a patient's HER2+ advanced breast cancer has progressed further on HER2-targeted therapy and if the patient had not received **trastuzumab emtansine (T-DM1; Kadcyla),** then **trastuzumab emtansine (T-DM1; Kadcyla)** can be given. It appears that, for HER2+ patients who have received multiple previous lines of therapy, **trastuzumab emtansine (T-DM1; Kadcyla)** can still be of major benefit. In the Phase 3 TH3RESA clinical trial, 602 HER2+ pretreated MBC patients were randomly assigned **trastuzumab emtansine (T-DM1; Kadcyla)**, 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 **trastuzumab emtansine (T-DM1; Kadcyla)** 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[35, PMID:24793816]:** ***http://www.sciencedaily.com/releases/2015/12/151211124307.htm***

- **Trastuzumab (Herceptin) (or trastuzumab and hyaluronidase-oysk (Herceptin Hylecta) or a biosimilar)** with chemotherapy.

- **Trastuzumab (Herceptin) (or trastuzumab and hyaluronidase-oysk (Herceptin Hylecta) or a biosimilar) with lapatinib (Tykerb).**

- **Lapatinib (Tykerb) with chemotherapy.**

- **Trastuzumab (Herceptin) (or trastuzumab and hyaluronidase-oysk (Herceptin Hylecta) or a biosimilar) and pertuzumab (Perjeta),** with or without chemotherapy *(if the patient has previously taken **trastuzumab (Herceptin) and chemotherapy without pertuzumab (Perjeta)).*** Note that **Phesgo** (an injectable combination of Herceptin, Perjeta, and hyaluronidase-zzxf) can be given, with or without chemotherapy.

- **Trastuzumab and hyaluronidase-oysk (Herceptin Hylecta)** alone *(if the patient has received one or more courses of chemotherapy for MBC).*

- A clinical trial is also an option.

If a US patient's cancer has microsatellite instability-high (MSI-H), mismatch repair deficient (dMMR) characteristics (which are very rare), or is tumor mutational burden-high (TMB-H), and if the patient has progressed on prior therapy and has no satisfactory treatment options, **pembrolizumab** (**Keytruda;** a PD-1 inhibitor), is an FDA-approved option. This therapy was also approved for patients with unresectable or metastatic TMB-H solid tumors. **Dostarlimab-gxly (Jemperli)** has also been FDA-approved for the treatment of adult patients with dMMR recurrent or advanced solid tumors, as determined by an FDA-approved test, who have progressed on or following previous treatment and who have no satisfactory alternative options.

If a US patient's cancer has a neurotrophic receptor tyrosine kinase (*NTRK*) gene fusion without a known acquired resistance mutation, and if there has been progression on prior therapy with no satisfactory treatment options, **larotrectinib (Vitrakvi)** and **entrectinib (Rozlytrek)** - oral tyrosine kinase inhibitors that act as an "on" or "off" switch in many cellular functions – are FDA-approved options. *NTRK* fusions are extremely rare, occurring in only about 0.5–1% of common cancers. Additional information is contained in the chapter, *"Approved Therapies Based Upon Tumor Characteristics."*

GUIDELINES FOR HER2+, HORMONE RECEPTOR-NEGATIVE MBC PATIENTS IN CANADA:

Other than the following, the author was unable to locate specific information relative to HER2+ MBC patients in Canada:

Patients who have not had previous anti-HER2 therapy or chemotherapy for their metastatic disease should receive a combination of **trastuzumab (Herceptin), pertuzumab (Perjeta), and docetaxel (Taxotere)**. **From:** ***https://www.newswire.ca/news-releases/health-canada-approves-perjeta-a-new-first-in-class-targeted-therapy-for-the-treatment-of-her2-positive-metastatic-breast-cancer1-512312341.html***

A second - (or later-) line therapy is the combination of the oral drug **tucatinib (Tukysa)** with **capecitabine (Xeloda)** and trastuzumab **(Herceptin) (or an approved biosimilar)** for HER2+ Canadian MBC patients (including those with brain metastases) who received one or more HER2-directed therapies in the metastatic setting. **From:** ***https://breastcancer-news.com/2020/08/17/australia-tga-approves-tukysa-trastuzumab-capecitabine-combo-therapy-advanced-her2-positive-breast-cancer/?utm_source=Breast+Cancer+News&utm_campaign=892e985cec-RSS_MONDAY_EMAIL_CAMPAIGN_US&utm_medium=email&utm_term=0_ea3614260e-892e985cec-73234445***

GUIDELINES FOR HER2+, HORMONE RECEPTOR-NEGATIVE MBC PATIENTS GOVERNED BY NICE

The European Society for Medical Oncology (ESMO) provides guidelines for treatment of people with MBC. The patient version can be found here: ***https://www.esmo.org/living-guidelines/esmo-metastatic-breast-cancer-living-guideline.***

First-Line Therapy for HER2+, Hormone Receptor Negative-Patients Governed by Nice:

The combination of **trastuzumab (Herceptin) (or a biosimilar), pertuzumab (Perjeta), and docetaxel (Taxotere)** is recommended for patients who have not had previous anti-HER2 therapy or chemotherapy for their metastatic disease.

- **Trastuzumab (Herceptin) (or a biosimilar) in combination with paclitaxel (Taxol)** is recommended as an option for HER2+

patients who have not received chemotherapy for MBC and in whom anthracycline treatment is inappropriate.

Subsequent Therapies for HER2+, Hormone Receptor-Negative Patients Governed by NICE:

- **Trastuzumab emtansine (T-DM1; Kadcyla)** is recommended as an option for patients who previously received trastuzumab (Herceptin) and a taxane, either separately or in combination.

- **Fam-trastuzumab deruxtecan-nxki (T-DXd; Enhertu)** has received European Union (EU) approval for use in adults with unresectable or HER2+ MBC treated with a prior anti-HER2-based regimen.

- **Tucatinib (Tukysa)** is an option for HER2+ MBC patients who have been treated with two or more anti-HER2 therapies.

- **Eribulin (Halaven)** is recommended as an option for MBC patients after they have progressed on at least 2 chemotherapy regimens (which may include an anthracycline or a taxane, and capecitabine (Xeloda).

- **Trastuzumab (Herceptin)** (or a biosimilar) alone is recommended as an option for patients who have received at least two chemotherapy regimens for MBC. Prior chemotherapy must have included at least an anthracycline and a taxane where these treatments are appropriate.

- For patients who progressed on **trastuzumab (Herceptin)**, treatment with **trastuzumab (Herceptin)** should be changed to a different regimen unless the progression is solely in the brain or meninges, in which case **trastuzumab (Herceptin)** should be continued. **From:** ***https://pathways.nice.org.uk/pathways/advanced-breast-cancer#path=view%3A/pathways/advanced-breast-cancer/managing-advanced-breast-cancer.xml&content=view-node%3Anodes-hrneg-and-her2pos***

GUIDELINES FOR HER2+, HORMONE RECEPTOR-NEGATIVE MBC PATIENTS IN EUROPE (OTHER THAN NICE)

Initial Therapy:
HER2+, hormone receptor-negative patients without chemotherapy contraindications should receive **docetaxel (Taxotere)** or **paclitaxel (Taxol)** in combination with **trastuzumab (Herceptin)** and **pertuzumab (Perjeta).**

For patients with chemotherapy contraindications, **trastuzumab (Herceptin)** alone or **trastuzumab (Herceptin)** with **pertuzumab (Perjeta)** may be used. If the chemotherapy contraindication is specific to taxanes, **capecitabine (Xeloda)** or **vinorelbine (Navelbine)** can be considered along with **trastuzumab (Herceptin)** or **trastuzumab (Herceptin)** plus **pertuzumab (Perjeta).**

Second-Line Treatment After Initial Therapy Fails:
Fam-trastuzumab deruxtecan-nxki (T-DXd; Enhertu) alone is a highly recommended option for patients who have received one or more prior anti-HER2-based regimens.

Patients with active brain metastases for whom local intervention is indicated are eligible for resection with or without stereotactic radiotherapy or whole-beam radiation therapy based on the number of active brain metastases.

Third-Line Treatment and Beyond:
Third-line treatment and beyond recommendations are the same for patients with active brain metastases; however, in patients without active brain metastases, **trastuzumab emtansine (T-DM1; Kadcyla)** can be considered in the third-line setting, followed by either **lapatinib (Tykerb)** with **trastuzumab (Herceptin), trastuzumab (Herceptin)** with chemotherapy, **margetuximab (Margenza)** with chemotherapy, or **neratinib (Nerlynx)** with chemotherapy in subsequent lines of therapy. **From:** ***https://www.onclive.com/view/esmo-guidelines-recommend-personalized-treatment-and-multidisciplinary-decision-making-in-breast-cancer?fbclid=IwAR1g8ETQnQSVRfyoptCD853vdBIX8FgtXvKKT_gl7GAkQYnGkwatoeQyjQU***

GUIDELINES FOR HER2+, HORMONE RECEPTOR-NEGATIVE MBC PATIENTS IN AUSTRALIA are ambiguous, although it is assumed that they adhere to the international standard of care which is a combination

of **trastuzumab (Herceptin), pertuzumab (Perjeta), and a taxane as first-line therapy. Trastuzumab emtansine (T-DM1; Kadcyla)** is named as a follow-up treatment after progression, and **lapatinib (Tykerb)** is also acknowledged as a viable therapy. **From:** ***https://www.bcna.org.au/media/wyjp1yey/hah_her2-positive-mbc_2019.pdf***

A second- (or later-) line therapy is the combination of the oral drug **tucatinib (Tukysa)** with **capecitabine (Xeloda)** and **trastuzumab (Herceptin)** (or an approved biosimilar) for HER2+ Australian MBC patients (including those with brain metastases) who received one or more HER2-directed therapies in the metastatic setting. **From:** ***https://breastcancer-news.com/2020/08/17/australia-tga-approves-tukysa-trastuzumab-capecitabine-combo-therapy-advanced-her2-positive-breast-cancer/?utm_source=Breast+Cancer+News&utm_campaign=892e985cec-RSS_MONDAY_EMAIL_CAMPAIGN_US&utm_medium=email&utm_term=0_ea3614260e-892e985cec-73234445***

Guidelines for patients living in resource-constrained countries are provided by the American Society of Clinical Oncology (ASCO): ***https://ascopubs.org/doi/10.1200/GO.23.00285***

ADDITIONAL INFORMATION FOR HER2+, HORMONE RECEPTOR-NEGATIVE PATIENTS IRRESPECTIVE OF LOCATION:

Surgical Removal of the Primary Tumor in HER2+ MBC Patients: Many patients with advanced HER2+ breast cancer have had tremendous responses to the new targeted therapies, and a subset of these patients have lived long enough that their primary breast cancer tumors began causing problems. Although surgeons have generally avoided operating on MBC patients due to their likelihood of dying of their metastatic disease, it was hypothesized that many HER2+ patients have been doing so well that surgery might make sense. To assess the impact of primary tumor resection on survival among 3,231 HER2+ Stage IV patients, researchers analyzed data from 2010 to 2012 in the National Cancer Database. Of these patients, 35% had undergone surgery for their primary breast cancer, and the results showed that these patients had a 44% survival improvement compared with similar patients who did not have surgery. Furthermore, the survival benefit appeared to be independent of other factors typically associated with outcomes, such as co-morbidities and tumor size. (That said, it is possible that patients who underwent surgery may have been generally healthier and therefore were better surgical candidates). In summary, HER2+ MBC patients who are doing well may wish to discuss the

possibility of surgically removing their primary breast tumor with their medical teams. **From:** ***https://www.healio.com/hematology-oncology/breast-cancer/news/online/%7Bd7e88e7b-a31a-419b-8b7c-8bc0721644a1%7D/surgery-prolongs-survival-in-her2-positive-advanced-breast-cancer?page=1***

Caution Regarding CNS Metastasis: Patients with HER2+ 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 **trastuzumab (Herceptin)**. **From[37, 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- and/or who have not received a taxane. **From[38, 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 (ARs), 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 ARs, up to 27% of HER2+ patients may have an amplification of *FGFR1* and/or chromosome 11q. This is significant because therapies are being developed that target these factors. **From:** ***https://www.nccn.org/patients/guidelines/content/PDF/stage_iv_breast-patient.pdf***

For additional information, suggested sections include:

Personalized Medicine

Chemotherapy

Targeted Therapy

Research and Potentially Helpful Therapies

9. Triple Negative MBC & Related Therapies

The National Comprehensive Cancer Network (NCCN) provides guidelines for treatment of people with MBC. The patient version can be found here: ***https://www.nccn.org/patients/guidelines/content/PDF/stage_iv_breast-patient.pdf***. More information is available in the professional guidelines: (***https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf***).
You can create a free account to view the professional guidelines. The information provided below is current as of 2023. Please see the above guidelines for the most recent updates.
In addition, the American Society of Clinical Oncology (ASCO) also provides guidelines.

Patients whose breast cancer neither expresses hormone receptors nor has HER2 protein amplification have what is called "Triple Negative Breast Cancer" (**TNBC**) or **Basal-Like** breast cancer. Chemotherapy remains the mainstay of TNBC treatments. However, targeted therapies have been approved, including sacituzumab govitecan (Trodelvy). Treatments for patients with specific biomarkers include fam-trastuzumab deruxtecan-nxki (T-DXd; Enhertu) for HER2-low TNBC; the PARP inhibitors, olaparib (Lynparza) and talazoparib (Talzenna) for TNBC with *BRCA1/2* germline mutations; and pembrolizumab (Keytruda) for PD-L1+ (CPS 10 or +) TNBC. 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 receptor-positive group, and therefore be potential candidates for hormonal therapy as described in the section entitled *Types of Breast Cancer.* **From[39, PMID:21147047; 40; 41]: *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.

CLASSES OF DRUGS USED TO TREAT METASTATIC TNBC

- **Monoclonal Antibodies:** Antibodies are an integral part of the body's immune system. Normally the body creates antibodies in response to an "antigen" (a germ that has entered the body, or a specific protein). Antigens are molecules capable of stimulating an immune response, and each antigen has distinct surface features that result in specific responses. Antibodies attach to the antigen in order to mark it for destruction by the immune system. When given to a patient, specific antibodies will attach to matching antigens in much the same way that a key fits a lock. Monoclonal antibodies are laboratory-produced molecules that serve as substitute antibodies that can restore, enhance or mimic the immune system's attack on cancer cells. They are designed to bind to antigens that are generally more numerous on the surface of cancer cells than healthy cells.

- **Antibody Drug Conjugates (ADCs):** ADCs comprise an antibody that recognizes a target on the cancer cell surface linked to a chemotherapy payload that is released when the antibody binds to that target. In an ideal world, these cell-surface targets would only be expressed on cancer cells, but there can be lower expression of them on normal cells, contributing to side effects due to interactions with normal cells. The goal of ADCs is to deliver chemo where it's needed and not everywhere in the body. Because ADCs are more specific than chemotherapy, they tend to be better tolerated by patients. However, the chemotherapy molecule can "fall off" the ADC and be released into the bloodstream, leading to side effects similar to traditional chemotherapies. Researchers are working to improve ADCs so that they release their chemotherapy payload only where needed. Additionally, some ADCs can cause antibody-specific and sometimes serious side effects such as lung damage (interstitial lung disease or pneumonitis). It's important to

be aware of the side effects associated with specific ADCs (for example fam-trastuzumab deruxtecan-nxki (T-DXd; Enhertu) versus sacituzumab govitecan (Trodelvy)), as they can differ significantly.

- **PD-1/PD-L1 Inhibitors are a type of monoclonal antibody.** PD-1 is a "checkpoint protein" on specific immune cells called T cells. It normally acts as a type of "off switch" that helps keep T cells from attacking other cells in the body. It does this when it attaches to PD-L1, a protein on some normal (and cancer) cells. When PD-1 binds to PD-L1, it basically tells the T cell to leave the other cell alone. Some cancer cells have large amounts of PD-L1, which helps them evade immune attack. Monoclonal antibodies that target either PD-1 or PD-L1 can block this binding, therefore boosting the immune system's response against cancer cells.

- **Chemotherapy ("chemo") drugs:** Cells within the body continually grow, divide, and die. Cancer cells tend to divide and form new cells more quickly than normal cells, making them more vulnerable to chemotherapy drugs. Chemotherapy drugs target cells at different phases of the process of forming new cells, called the "cell cycle." But because chemotherapy drugs can't distinguish between healthy cells and cancer cells, normal cells are damaged along with the cancer cells, causing side effects. Each time chemo is given, it means trying to find a balance between killing the cancer cells in order to cure or control the disease, and sparing the normal cells to lessen side effects.

- **Bone-directed Therapies:** Patients with **bone metastases** should receive a bone-directed therapy such as **denosumab (Xgeva or Prolia),** which is given by injection**,** or **zoledronic acid (Zometa),** which is administered by infusion, in addition to their cancer-directed therapy. These drugs help to prevent fractures and other cancer related bone problems in adults with cancer that has spread to the bones.

Sequence of Therapy for TNBC MBC Patients in the US:

If the patient's tumor has immune cells on or near it that are PD-L1 positive, then the patient should receive a combination of **pembrolizumab (Keytruda) and chemotherapy**. This combination was based upon the KEYNOTE-355 trial which randomized TNBC MBC patients who had not previously taken

chemotherapy in the metastatic setting to receive either **pembrolizumab (Keytruda)** plus chemotherapy or chemotherapy alone. The median progression-free survival was 9.7 months for patients taking the combination vs. 5.6 months for patients taking chemotherapy only. A test called PD-L1 IHC 22C3 pharmDx has been FDA-approved as a companion diagnostic for selecting patients with TNBC to be eligible for the **pembrolizumab (Keytruda)** plus chemotherapy regimen. **From:** ***https://www.fda.gov/drugs/drug-approvals-and-databases/fda-grants-accelerated-approval-pembrolizumab-locally-recurrent-unresectable-or-metastatic-triple***

If the PD-L1 positive cancer progresses:

- An antibody-drug conjugate called **fam-trastuzumab deruxtecan-nxki (T-DXd; Enhertu)** has been approved for TNBC MBC patients whose HER2 expression is considered to be "HER2-low," (IHC 1+, or IHC 2+ with negative results on in situ hybridization) and who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy.

- A PARP inhibitor **(talazoparib (Talzenna) or olaparib (Lynparza))** has been approved for TNBC patients who harbor a *BRCA1* or *BRCA2* mutation and who have received at least one prior chemotherapy in the neoadjuvant, adjuvant, or metastatic setting.

- After undergoing 2 lines of therapy (at least one of which was for metastatic disease), TNBC MBC patients are eligible to receive **sacituzumab govitecan-hziy (Trodelvy)** (below), or they may elect to enroll in a clinical trial at any time during the course of their treatment.

If the patient's tumor-related immune cells are PD-L1 negative:

- An antibody-drug conjugate called **fam-trastuzumab deruxtecan-nxki (T-DXd; Enhertu)** has been approved for TNBC MBC patients whose HER2 expression is

considered to be "HER2-low," (IHC 1+, or IHC 2+ with negative results on in situ hybridization) and who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within six months of completing adjuvant chemotherapy.

- A PARP inhibitor **(talazoparib (Talzenna) or olaparib (Lynparza))** has been approved for TNBC patients who harbor a *BRCA1* or *BRCA2* mutation and who have received at least one prior chemotherapy in the neoadjuvant, adjuvant, or metastatic setting.

- Sequential **single-agent chemotherapy** is an option, as is enrolling in a clinical trial at any point during treatment.

NOTE: After undergoing 2 lines of therapy, all TNBC MBC patients are eligible to receive sacituzumab govitecan-hziy (Trodelvy) (below).

Third-line therapy and beyond for all TNBC MBC patients:
For third- or later-line therapy for TNBC patients, **sacituzumab Govitecan-hziy (Trodelvy)** was FDA-approved in April 2020 for the treatment of adult TNBC MBC patients who have received at least two prior therapies for their metastatic disease. **Sacituzumab govitecan-hziy (Trodelvy)**, which is administered intravenously, consists of the chemotherapy drug irinotecan linked with an antibody targeted against TROP-2, a cell-surface protein that is expressed in more than 90% of TNBC. Approval was based upon a Phase 1/2 trial of 108 TNBC MBC patients with a median of three prior lines of therapy (80% of whom had visceral metastases). The results of the study determined that the median progression-free survival (PFS) was 5.5 months and the median overall survival (OS) was 13.0 months. Final analysis from the confirmatory Phase 3 ASCENT trial showed better median PFS with sacituzumab govitecan-hziy (Trodelvy) compared to treatment of physician's choice (4.8 months vs 1.7 months) and better OS (11.8 months vs 6.9 months), respectively. As reported at ASCO 2024 (abstract #1102), data from a Phase 2 dose expansion cohort (NCT04039230) showed that sequential administration of sacituzumab govitecan-hziy (Trodelvy) followed by the PARP inhibitor talazoparib (Talzenna) provided a median PFS of 6.2 months and median OS of 18.0 months. In a previous study, giving

these two drugs at the same time produced unacceptable toxicity; however, giving them sequentially was safer and showed efficacy. **From:** ***https://www.oncnursingnews.com/web-exclusives/fda-approves-sacituzumab-govitecan-for-triplenegative-breast-cancer and https://pubmed.ncbi.nlm.nih.gov/38422473/***

If a US patient's cancer has microsatellite instability-high (MSI-H), mismatch repair deficient (dMMR) characteristics (which are very rare), or is tumor mutational burden-high (TMB-H), and if the patient has progressed on prior therapy and has no satisfactory treatment options, **pembrolizumab (Keytruda)** (a PD-1 inhibitor), is an FDA-approved option. This therapy was also approved for patients with unresectable or metastatic TMB-H solid tumors. **Dostarlimab-gxly (Jemperli)** has also been FDA-approved for the treatment of adult patients with dMMR recurrent or advanced solid tumors, as determined by an FDA-approved test, who have progressed on or following previous treatment and who have no satisfactory alternative options.

If a US patient's cancer has a neurotrophic receptor tyrosine kinase (*NTRK*) gene fusion without a known acquired resistance mutation, and if there has been progression on prior therapy with no satisfactory treatment options, **larotrectinib (Vitrakvi)** and **entrectinib (Rozlytrek)** - oral tyrosine kinase inhibitors that act as an "on" or "off" switch in many cellular functions – are FDA-approved options. *NTRK* fusions are extremely rare, occurring in only about 0.5–1% of common cancers. Additional information is contained in the chapter, "Approved Therapies Based Upon Tumor Characteristics."

APPROVED THERAPIES FOR TNBC PATIENTS OUTSIDE THE US:

The European Society for Medical Oncology (ESMO) provides guidelines for treatment of people with MBC. The patient version can be found here: ***https://www.esmo.org/living-guidelines/esmo-metastatic-breast-cancer-living-guideline***.
The author endeavored to locate comprehensive guidelines for treatment information for TNBC MBC patients in Canada, Europe, and Australia, but they were either ambiguously worded or unobtainable from a reliable source. However, the NICE guidelines below (which

typically pertain to patients in England) were found, although patients governed by NICE guidelines are advised to verify and thoroughly discuss their options with their doctor.

NICE Guidelines Regarding Treatment Options for TNBC MBC Patients:

In May 2020, NICE expressed support for the combination of **atezolizumab (Tecentriq) and paclitaxel (Abraxane)** (as described above) as a frontline treatment for adult patients with unresectable locally advanced or metastatic PD-L1–positive TNBC. **From:** ***http://www.pharmatimes.com/news/nice_u-turn_backs_roches_tecentriq_for_triple_negative_breast_cancer_1340742***

In May 2022, NICE approved **pembrolizumab (Keytruda) with chemotherapy** in women with TNBC MBC whose tumor(s) is PD-L1 positive with a combined score greater than or equal to 10. They must also not have had chemotherapy for advanced disease, and they qualify for treatment if surgery is not possible to remove the tumor. **From:** ***https://www.theguardian.com/society/2022/may/25/women-in-england-with-breast-cancer-to-qualify-for-drug-that-buys-precious-extra-time-keytruda***

In July 2022, **sacituzumab govitecan-hziy (Trodelvy)** was approved for patients with TNBC MBC who have already received two or more systemic therapies, at least one of which had been for locally advanced or metastatic disease which can't be removed surgically.

For patients needing chemotherapy and who cannot take anthracycline-based chemotherapy, the following chemotherapy options should be offered in the sequence below:

- First line therapy should be single-agent **docetaxel (Taxotere)**
- Second line therapy should be single-agent **capecitabine (Xeloda) or vinorelbine (Navelbine)**
- Third line therapy should be single-agent **capecitabine (Xeloda) or vinorelbine (Navelbine)** (whichever was not used as second-line treatment).

Gemcitabine (Gemzar) in combination with **paclitaxel (Taxol)** is recommended as an option for treatment only when **docetaxel (Taxotere)** monotherapy or **docetaxel (Taxotere)** in combination with **capecitabine (Xeloda)** are also considered appropriate.

From:
https://pathways.nice.org.uk/pathways/advanced-breast-cancer#path=view%3A/pathways/advanced-breast-cancer/managing-advanced-breast-cancer.xml&content=view-node%3Anodes-triple-negative-disease

European Guidelines for TNBC MBC Patients in European Countries Not Governed by NICE:

Patients with PD-L1–positive metastatic TNBC should receive **atezolizumab (Tecentriq)** plus **paclitaxel (Abraxane)**, or **pembrolizumab (Keytruda)** plus chemotherapy.

Patients with *BRCA*-mutated TNBC should receive either chemotherapy, or a PARP inhibitor **(olaparib (Lynparza)** or **talazoparib (Talzenna)).**

Patients with PD-L1–negative, *BRCA* wild-type TNBC should receive anthracycline/taxane–based therapy, a taxane with **bevacizumab (Avastin)**, or **capecitabine (Xeloda)** with **bevacizumab (Avastin)** if organ failure is imminent. (If organ failure is not imminent, then patients should receive a taxane or anthracycline monotherapy).

Upon progression, **sacituzumab govitecan-hziy (Trodelvy)** or chemotherapy is indicated for all patients, followed by chemotherapy with **eribulin (Halaven)**, **capecitabine (Xeloda)**, or **vinorelbine (Navelbine)**.

From:
https://www.onclive.com/view/esmo-guidelines-recommend-personalized-treatment-and-multidisciplinary-decision-making-in-breast-cancer?fbclid=IwAR1g8ETQnOSVRfyoptCD853vdBIX8FgtXvKKT_gl7GAkQYnGkwatoeQyjQU
Guidelines for patients living in resource-constrained countries are provided by the American Society of Clinical Oncology (ASCO): ***https://ascopubs.org/doi/10.1200/GO.23.00285***

ADDITIONAL INFORMATION FOR HER2-, HORMONE RECEPTOR-NEGATIVE PATIENTS IRRESPECTIVE OF LOCATION:

All 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.

Eribulin (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 **eribulin (Halaven)** versus **capecitabine (Xeloda)**. Additional Phase 3 trials substantiated the effectiveness of **eribulin (Halaven)** over standard treatment. The two studies showed an overall improvement in survival of 5 months for metastatic breast cancer patients with TNBC. **From[42, PMID:28141030]:** ***http://www.sciencedaily.com/releases/2014/11/141102212054.htm***

Platinum Chemotherapy (such as carboplatin (Paraplatin) 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 poly ADP-ribose polymerase (PARP) 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[43; 44; PMID:25476537] and **[194, PMID:23012302]:** ***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/***

Although a patient's HER2 status may be negative as per their pathology report, in some cases HER2-directed treatment may be viable, and this situation is being studied. For example, the drug **fam-trastuzumab deruxtecan-nxki (T-DXd; Enhertu)** elicited a response in patients with HER2-low expression (IHC value +1 or +2 and negative for HER2 gene amplification by in situ hybridization [ISH]) whose in situ hybridization test results classified their status as

HER2-. Additional information about **fam-trastuzumab deruxtecan-nxki (T-DXd; Enhertu)** is located under *Research and Potential Therapies for HER2- (or Low) MBC.*

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 AR in much the same way that estrogen suppression therapy inhibits the ER in ER-positive breast cancers. Furthermore, a study in the journal *Molecular Cancer Therapeutics* shows that only about 1% 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 ARs in the section entitled*, Research and Potential Therapies for All Categories of Breast Cancer.*
From[49, PMID:26201402]: ***http://medicalxpress.com/news/2015-02-low-androgen-triple-negative-breast-cancer-anti-androgen.html***

In addition to potentially having ARs, 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 that 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[50, PMID:25144278]**

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+ MBC & Related Therapies

The National Comprehensive Cancer Network (NCCN) provides guidelines for treatment of people with MBC. The patient version can be found here: ***https://www.nccn.org/patients/guidelines/content/PDF/stage_iv_breast-patient.pdf***. More information is available in the professional guidelines: (***https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf***). You can create a free account to view the professional guidelines. The information provided below is current as of 2023. Please see the above guidelines for the most recent updates.

In addition, the American Society of Clinical Oncology (ASCO) also provides guidelines.

About half of HER2+ 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 that are both HR+ and HER2+ (often referred to as "Triple Positive") can behave differently than might 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[51, 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.

Triple-positive MBC patients may be candidates for hormonal therapy drugs (including drugs that can be used in combination with them) as well as HER2-directed drugs. For important background information about treatments regarding hormone receptor-positive MBC and HER2+ MBC, please read the chapters entitled, *"Hormone Receptor-Positive/HER2- MBC & Related Therapies*" and "*HER2+/Hormone Receptor-Negative MBC & Related Therapies."*

Patients with **bone metastases** should receive a bone-directed therapy such as **denosumab (Xgeva)** or **zoledronic acid (Zometa)** in addition to their other therapy.

NCCN GUIDELINES FOR HORMONE RECEPTOR-POSITIVE, HER2+ MBC PATIENTS IN THE US

NCCN 2019 Guidelines for patients in the US stated that **hormonal (endocrine) therapy without HER2-targeted therapy may be considered under specific circumstances:** the patient's cancer is only in the bones (or if it's in an organ and there are no symptoms), and it appears that the patient is likely to respond to endocrine therapy due to a long disease-free interval, has limited sites of disease, a slow disease progression ("indolent disease"), and the patient is older in age. *<**Author's note:** NCCN 2020 Guidelines did not mention this option.>*

Hormonal therapy options for eligible triple-positive patients in the US are listed immediately below with the understanding that premenopausal women - as well as men - should also take a luteinizing hormone-releasing hormone (LHRH) agonist such as **goserelin (Zoladex)**, **leuprolide (Lupron),** or **triptorelin (Trelstar)** to suppress the production of specific hormones in the body (this is optional when taking tamoxifen (Nolvadex) or toremifene (Fareston)). If the cancer progresses on initial endocrine therapy, another type of endocrine therapy may be considered, or a HER2-targeted therapy (with or without hormonal therapy) may be taken.

- An Aromatase Inhibitor (AI) such as **letrozole (Femara), anastrozole (Arimidex), or exemestane (Aromasin)** .
- **Fulvestrant (Faslodex) with or without anastrozole (Arimidex) or letrozole (Femara).**

- **Tamoxifen (Nolvadex) or toremifene (Fareston).**

HER2-TARGETED THERAPY FOR TRIPLE POSITIVE PATIENTS IN THE US MAY BE TAKEN ALONE, OR IN COMBINATION WITH EITHER CHEMOTHERAPY OR HORMONAL THERAPY AS DESCRIBED BELOW. A CLINICAL TRIAL IS ALSO AN OPTION.

HER2-Targeted Therapy Options for Triple-Positive Patients in the US with or without Chemotherapy:

- **Trastuzumab (Herceptin)** (or a biosimilar), **or trastuzumab and hyaluronidase-oysk (Herceptin Hylecta) (the subcutaneous injectable form of Herceptin) with pertuzumab (Perjeta) and a taxane** chemotherapy. According to NCCN 2020 Guidelines, this "triplet" is the preferred therapy for triple-positive patients. *(That said, frontline treatment for HER2+ MBC patients was researched in the Phase 2 PERNETTA trial, which randomized 210 previously untreated HER2+ MBC patients [some of whom were triple positive] to receive either* ***trastuzumab (Herceptin)****,* ***pertuzumab (Perjeta)****, and chemotherapy ["Group 1"] vs.* ***trastuzumab (Herceptin)*** *and* ***pertuzumab (Perjeta)*** *without chemotherapy ["Group 2"]. Patients whose disease progressed were given* ***trastuzumab emtansine (T-DM1; Kadcyla)*** *in the second-line setting. Results announced in July 2019 indicated that the 2-year overall survival [OS] was similar in both Groups, although the progression-free survival [PFS] was better in Group 1. For HER2+, hormone receptor-positive patients in Group 1, the median PFS was 23.7 months vs. 8.3 months for Group 2, and the OS was very close – 74.2% vs. 75%.* ***The researchers indicated that frontline trastuzumab (Herceptin) and pertuzumab (Perjeta) without chemotherapy [but with endocrine therapy] may be considered for triple-positive patients with low-to-intermediate tumor burden, especially since treatment toxicity is considerably reduced).*** **From:** ***https://www.targetedonc.com/publications/targeted-therapy-news/2019/july-2019/patients-with-mbc-have-reduced-toxicity-***

burden-with-dual-her2targeted-therapy-in-the-front-line
(Note that **Phesgo** - an injectable combination of **Herceptin, Perjeta, and hyaluronidase-zzxf** - can be substituted for the **trastuzumab (Herceptin)/pertuzumab (Perjeta)** combination).

For triple-positive patients who have taken the triplet combination of **trastuzumab (Herceptin), pertuzumab (Perjeta),** and a taxane: once the taxane is dropped after several months, it's recommended that endocrine therapy be given along with **trastuzumab (Herceptin)** and **pertuzumab (Perjeta)** as maintenance treatment.

Additional Lines of Treatment for HER2+, Hormone Receptor-Positive MBC Patients in the US *(these are described more fully in the chapter "HER2+/Hormone Receptor-Negative MBC & Related Therapies"):*

- **Fam-trastuzumab deruxtecan-nxki (T-DXd; Enhertu),** which has shown statistically significant improvement in progression-free survival (PFS) when compared with **trastuzumab emtansine (T-DM1; Kadcyla)** below as second-line treatment for HER2+ MBC, has been FDA-approved for HER2+ adult patients who have received a prior anti-HER2-based regimen either in the metastatic setting, or in the neoadjuvant or adjuvant setting and have developed disease recurrence during or within 6 months of completing therapy. At a median follow-up of about 16 months in the DESTINY-Breast03 Phase 3 study, median PFS was not reached with **Fam-trastuzumab deruxtecan-nxki (T-DXd; Enhertu)** and was 6.8 months with **trastuzumab emtansine (T-DM1; Kadcyla)**. The benefit was observed across all prespecified subgroups, including patients with brain metastases. **From:** ***https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-regular-approval-fam-trastuzumab-deruxtecan-nxki-breast-cancer***

- **Trastuzumab emtansine (T-DM1; Kadcyla)** may confer an overall survival (OS) of 29.9 months when used as a second-line therapy, which is superior to lapatinib (Tykerb) plus capecitabine (Xeloda), which provided an OS of 25.9 months. **Trastuzumab emtansine (T-DM1; Kadcyla)** can

also be a viable first-line therapy in patients for whom **trastuzumab (Herceptin), pertuzumab (Perjeta),** and a taxane might be too toxic). **From[34, PMID:26656517]:** ***http://www.jnccn.org/content/13/12/1475.full*** and ***https://www.kadcyla.com/***

- Another second - (or later-) line therapy is the combination of the oral drug **tucatinib (Tukysa) with capecitabine (Xeloda) and trastuzumab (Herceptin) (or trastuzumab and hyaluronidase-oysk (Herceptin Hylecta)** or an approved biosimilar) for HER2+ MBC patients (including those with brain metastases) who received one or more HER2-directed therapies in the metastatic setting.

- Yet another option is **margetuximab (Margenza) in combination with chemotherapy** for HER2+ MBC patients who have received two or more prior anti-HER2 regimens, at least one of which was for metastatic disease.

- Another option for third- (or later-) line therapy is the **combination of neratinib (Nerlynx) and capecitabine (Xeloda)**, which was FDA-approved in Feb. 2020 for HER2+ MBC patients who received two or more prior anti-HER2 based regimens in the metastatic setting.

- If a patient's HER2+ advanced breast cancer has progressed further on HER2-targeted therapy and if the patient had not received **trastuzumab emtansine (T-DM1; Kadcyla),** then this drug can be given. It appears that, for HER2+ patients who have received multiple previous lines of therapy, trastuzumab emtansine (T-DM1; Kadcyla) can still be of major benefit. In the Phase 3 TH3RESA clinical trial, 602 HER2+ pretreated MBC patients were randomly assigned **trastuzumab emtansine (T-DM1; Kadcyla)** 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 **trastuzumab emtansine (T-DM1; Kadcyla)** 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[35, PMID:24793816]:**

http://www.sciencedaily.com/releases/2015/12/151211124307.htm

- **Trastuzumab (Herceptin) (or trastuzumab and hyaluronidase-oysk (Herceptin Hylecta) or a biosimilar)** with chemotherapy.

- **Trastuzumab (Herceptin) (or trastuzumab and hyaluronidase-oysk (Herceptin Hylecta) or a biosimilar) with lapatinib (Tykerb).**

- **Lapatinib (Tykerb) with chemotherapy.**

- **Trastuzumab (Herceptin) (or trastuzumab and hyaluronidase-oysk (Herceptin Hylecta) or a biosimilar) and pertuzumab (Perjeta),** with or without chemotherapy (if the patient has previously taken trastuzumab (Herceptin) and chemotherapy without pertuzumab (Perjeta)). Note that **Phesgo** (an injectable combination of **Herceptin, Perjeta,** and **hyaluronidase-zzxf)** can be given, with or without chemotherapy.

- **Trastuzumab and hyaluronidase-oysk (Herceptin Hylecta)** alone (if the patient has received one or more courses of chemotherapy for MBC).

- A clinical trial is also an option.

HER2-Targeted Therapy Options in Combination with Hormonal Therapy for Triple-Positive Patients in the US:

As mentioned above, premenopausal women - as well as men - should take a luteinizing hormone-releasing hormone agonist while taking hormonal therapy, although this is optional when taking tamoxifen (Nolvadex) or toremifene (Fareston)).

- An aromatase inhibitor with **trastuzumab (Herceptin)** (or **trastuzumab and hyaluronidase-oysk (Herceptin Hylecta)** or a biosimilar).
- An aromatase inhibitor with **Tykerb,** with or without **trastuzumab (Herceptin) (or trastuzumab and hyaluronidase-oysk (Herceptin Hylecta) or a biosimilar).**

- **Fulvestrant (Faslodex) with trastuzumab (Herceptin) (or trastuzumab and hyaluronidase-oysk (Herceptin Hylecta) or a biosimilar).**
- **Tamoxifen (Nolvadex) or toremifene (Fareston) with trastuzumab (Herceptin)** (or a **trastuzumab and hyaluronidase-oysk (Herceptin Hylecta)** or a biosimilar).
- **Trastuzumab (Herceptin)** (or trastuzumab and hyaluronidase-oysk (Herceptin Hylecta) or a biosimilar) **with pertuzumab (Perjeta)** and any one of the above hormonal therapies. Note that **Phesgo** (an injectable combination of **Herceptin, Perjeta, and hyaluronidase-zzxf**) can be substituted for the **trastuzumab (Herceptin)/pertuzumab (Perjeta)** combination.

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

If a US patient's cancer has microsatellite instability-high (MSI-H), mismatch repair deficient (dMMR) characteristics (which are very rare), or is tumor mutational burden-high (TMB-H), and if the patient has progressed on prior therapy and has no satisfactory treatment options, **pembrolizumab (Keytruda;** a PD-1 inhibitor), is an FDA-approved option. This therapy was also approved for patients with unresectable or metastatic TMB-H solid tumors. **Dostarlimab-gxly (Jemperli)** has also been FDA-approved for the treatment of adult patients with dMMR recurrent or advanced solid tumors, as determined by an FDA-approved test, who have progressed on or following previous treatment and who have no satisfactory alternative options.

Similar to the above, if a US patient's cancer has a neurotrophic receptor Tyrosine kinase (*NTRK*) gene fusion without a known acquired resistance mutation, and if there has been progression on prior therapy with no satisfactory treatment options, **larotrectinib (Vitrakvi)** and **entrectinib (Rozlytrek)** - oral tyrosine kinase inhibitors that act as an "on" or "off" switch in many cellular functions – are FDA-approved options. *NTRK* fusions are extremely rare, occurring in only about 0.5–1% of common cancers. Additional information is contained in the chapter, *"Approved Therapies Based Upon Tumor Characteristics."*

CANADIAN GUIDELINES FOR HER2+, HORMONE RECEPTOR-POSITIVE MBC PATIENTS are ambiguous, although it is

possible that the treatments for Canadian HER2+, hormone receptor-negative patients depicted in the chapter *"HER2+/Hormone Receptor-Negative MBC & Related Therapies"* also apply to triple-positive MBC patients in Canada.

That said, an approved second- (or later-) line therapy is the combination of the oral drug **tucatinib (Tukysa)** with **capecitabine (Xeloda)** and trastuzumab (**Herceptin) (or an approved biosimilar)** for HER2+ Canadian MBC patients (including those with brain metastases) who received one or more HER2-directed therapies in the metastatic setting. **From:** ***https://breastcancer-news.com/2020/08/17/australia-tga-approves-tukysa-trastuzumab-capecitabine-combo-therapy-advanced-her2-positive-breast-cancer/?utm_source=Breast+Cancer+News&utm_campaign=892e985cec-RSS_MONDAY_EMAIL_CAMPAIGN_US&utm_medium=email&utm_term=0_ea3614260e-892e985cec-73234445***

NICE GUIDELINES FOR HER2+, HORMONE RECEPTOR-POSITIVE MBC PATIENTS

The European Society for Medical Oncology (ESMO) provides guidelines for treatment of people with MBC. The patient version can be found here: ***https://www.esmo.org/living-guidelines/esmo-metastatic-breast-cancer-living-guideline***.

NICE Guidelines for First-Line Therapy for Hormone Receptor-Positive, HER2+ MBC Patients:

- The combination of **trastuzumab (Herceptin)** (or a biosimilar), **pertuzumab (Perjeta), and docetaxel (Taxotere)** is recommended for patients who have not had previous anti-HER2 therapy or chemotherapy for their metastatic disease.

- **Trastuzumab (Herceptin)** (or a biosimilar) **in combination with paclitaxel (Taxol)** is recommended as an option for HER2+ patients who have not received chemotherapy for MBC and in whom anthracycline treatment is inappropriate.

NICE Guidelines for Subsequent Lines of Therapy for Hormone Receptor-Positive, HER2+ MBC Patients:

- **Trastuzumab emtansine (T-DM1; Kadcyla)** is recommended as an option for patients who previously received **trastuzumab (Herceptin)** and a taxane, either separately or in combination.

- **Fam-trastuzumab deruxtecan-nxki (T-DXd; Enhertu)** has been granted conditional authorization in the UK as a monotherapy for the treatment of adult patients with unresectable or metastatic HER2+ breast cancer who have received two or more prior anti-HER2-based regimens.

- **Tucatinib (Tukysa)** is an option for HER2+ MBC patients who have been treated with two or more anti-HER2 therapies.

- **Eribulin (Halaven)** is recommended as an option for MBC patients after they have progressed on at least 2 chemotherapy regimens (which may include an anthracycline or a taxane, and capecitabine (Xeloda)).

- **Trastuzumab (Herceptin)** (or a biosimilar) alone is recommended as an option for patients who have received at least two chemotherapy regimens for MBC. Prior chemotherapy must have included at least an anthracycline and a taxane where these treatments are appropriate. It should also have included hormonal therapy in suitable estrogen receptor-positive patients.

- For patients who progressed on **trastuzumab (Herceptin)**, treatment with **trastuzumab (Herceptin)** should be changed to a different regimen unless the progression is solely in the brain or meninges, in which case **trastuzumab (Herceptin)** should be continued.

From:
https://pathways.nice.org.uk/pathways/advanced-breast-cancer#path=view%3A/pathways/advanced-breast-cancer/managing-advanced-breast-cancer.xml&content=view-node%3Anodes-hrneg-and-her2pos

EUROPEAN (OTHER THAN NICE) GUIDELINES FOR HER2+, HORMONE RECEPTOR-POSITIVE MBC PATIENTS

Initial Therapy:
Patients who have hormone receptor (HR)-positive, HER2+ disease without chemotherapy contraindications should receive **docetaxel (Taxotere)** or **paclitaxel (Taxol)**, **trastuzumab (Herceptin)**, and **pertuzumab (Perjeta)** followed by **trastuzumab (Herceptin), pertuzumab (Perjeta),** and endocrine therapy.

Patients with chemotherapy contraindications should receive **trastuzumab (Herceptin)** with or without **pertuzumab (Perjeta)** and endocrine therapy.

Second-Line Treatment After Initial Therapy Fails:
Fam-trastuzumab deruxtecan-nxki (T-DXd; Enhertu)alone is a highly recommended option for patients who have received one or more prior anti-HER2-based regimens.

Patients with active brain metastases for whom local intervention is indicated are eligible for resection with or without stereotactic radiotherapy or whole-beam radiation therapy based on the number of active brain metastases.

Third-Line Treatment and Beyond:
Third-line treatment and beyond recommendations are the same for patients with active brain metastases; however, in patients without active brain metastases, **trastuzumab emtansine (T-DM1; Kadcyla)** can be considered in the third-line setting, followed by either **lapatinib (Tykerb)** with **trastuzumab (Herceptin), trastuzumab (Herceptin)** with chemotherapy, **margetuximab (Margenza)** with chemotherapy, or **neratinib (Nerlynx)** with chemotherapy in subsequent lines of therapy.

From:
https://www.onclive.com/view/esmo-guidelines-recommend-personalized-treatment-and-multidisciplinary-decision-making-in-breast-cancer?fbclid=IwAR1g8ETQnQSVRfyoptCD853vdBIX8FgtXvKKT_gl7GAkQYnGkwatoeQyjQU

AUSTRALIAN GUIDELINES FOR HER2+, HORMONE RECEPTOR-POSITIVE MBC PATIENTS are indeterminate, although it is possible that the treatments for Australian HER2+, hormone receptor-negative patients described in the chapter *"HER2+/Hormone Receptor-Negative MBC & Related Therapies"* also apply to triple-positive MBC patients in Australia.

That said, an approved second- (or later-) line therapy is the combination of the oral drug **tucatinib (Tukysa)** with **capecitabine (Xeloda)** and **trastuzumab (Herceptin) (or an approved biosimilar)** for HER2+ Australian MBC patients (including those with brain metastases) who received one or more HER2-directed therapies in the metastatic setting. **From:** ***https://breastcancer-news.com/2020/08/17/australia-tga-approves-tukysa-trastuzumab-capecitabine-combo-therapy-advanced-her2-positive-breast-cancer/?utm_source=Breast+Cancer+News&utm_campaign=892e985cec-RSS_MONDAY_EMAIL_CAMPAIGN_US&utm_medium=email&utm_term=0_ea3614260e-892e985cec-73234445***

Guidelines for patients living in resource-constrained countries are provided by the American Society of Clinical Oncology (ASCO): https://ascopubs.org/doi/10.1200/GO.23.00285

ADDITIONAL INFORMATION FOR HER2+, HORMONE RECEPTOR-POSITIVE PATIENTS IRRESPECTIVE OF LOCATION:

For patients achieving a complete response, 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 response may be considered in some patients, particularly if additional treatments are available in case of progression. **From[52, PMID:PMC5834023]:** ***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 receptors and/or progesterone receptors 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+ breast cancers are positive for androgen receptors (ARs), 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+ breast cancers have an amplification of *FGFR1* and/or chromosome 11q. This is significant because therapies are being developed that specifically target these factors.

For additional information, suggested sections include:

Personalized Medicine for tumor testing and other options

Hormone Receptor-Positive/HER2- MBC & Related Therapies

HER2+/Hormone Receptor-Negative MBC & 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 are ER+/PR+ (hormone receptor positive, [HR+]) and HER2-.

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*.

Men with hormone receptor-positive, HER2- MBC are urged to read the chapter entitled, "*Hormone Receptor-Positive/HER2--MBC & Related Therapies"* for background information before reading the remainder of this chapter. Men with other cancer subtypes should instead refer to the respective chapter for their specific situation *(*either *"HER2+, Hormone Receptor-Negative MBC & Related Therapies," "Triple-Negative MBC and Related Therapies,"* or *"Hormone Receptor-Positive/HER2+ MBC & Related Therapies"*).

According to a large real-life study investigating 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 and responded in a comparable manner. **From:** ***http://www.cancer.gov/cancertopics/pdq/treatment/malebreast/Patient/page1***

Furthermore, targeted therapy medicines that target the *HER2* or *PIK3CA* genes, PD-L1 proteins, or mutations in the *BRCA1* or *BRCA2* genes may be used to treat advanced-stage or metastatic male breast cancer in the same way they are used to treat the disease in women.

International guidelines state that for hormone receptor-positive (HR+) human epidermal growth factor receptor 2-negative (HER2-) MBC patients, endocrine (hormonal) therapy in conjunction with a CDK4/6 inhibitor should be given as first-line treatment, except in case of acute visceral crisis (severe organ dysfunction). **From:** ***https://www.esmo.org/living-guidelines/esmo-metastatic-breast-cancer-living-guideline***

Although information is admittedly sparse regarding male breast cancer, metastatic or otherwise, the good news is that men are increasingly being distinctly studied with respect to therapeutic response, and therapeutic recommendations specifically geared towards men are being initiated. The first of these occurred in April 2019, when the FDA specifically approved the use of **palbociclib (Ibrance)** in combination with an aromatase inhibitor **(letrozole (Femara), anastrozole (Arimidex),** or **exemestane (Aromasin))** or with **fulvestrant (Faslodex)** as first-line therapy for men with hormone receptor-positive, HER2- MBC. **From:** ***https://www.pfizer.com/news/press-release/press-release-detail/u_s_fda_approves_ibrance_palbociclib_for_the_treatment_of_men_with_hr_her2_metastatic_breast_cancer#:~:text=Thursday%2C%20April%2004%2C%202019%20%2D,who%20are%20most%20in%20need.%E2%80%9D***

The sequence of providing hormonal (endocrine) therapy for HR+ HER2- male patients may vary, since much of it depends upon what - if any - hormonal therapy drugs were previously taken in the adjuvant or metastatic setting, and how recently they were taken. A luteinizing hormone-releasing hormone **(LHRH**) agonist (also known as a gonadotropin-releasing hormone [GnRH] agonist) such as **goserelin**

(Zoladex), leuprolide (Lupron), or **triptorelin (Trelstar)** is recommended for men who will be taking an aromatase inhibitor or **fulvestrant (Faslodex)** either with a CDK4/6 inhibitor or alone. The agonist works by suppressing the production of testosterone and estrogen.

First-Line Hormonal (Endocrine) and Targeted Treatment Options for Male Hormone Receptor-Positive, HER2- Patients in the US:

- The combination of a CDK4/6 inhibitor such as **palbociclib (Ibrance), ribociclib (Kisqali), or abemaciclib (Verzenio)** with either an aromatase inhibitor **(letrozole (Femara), anastrozole (Arimidex), or exemestane (Aromasin)),** or with **fulvestrant (Faslodex)** is the current standard-of-care as initial treatment, along with an LHRH agonist.
- An aromatase inhibitor alone (but with an LHRH agonist).
- **Fulvestrant (Faslodex)** with either **letrozole (Femara)** or **anastrozole (Arimidex)** (with an LHRH agonist).
- **Fulvestrant (Faslodex)** alone (but with an LHRH agonist).
- **Tamoxifen (Nolvadex) or toremifene (Fareston)** with or without an LHRH agonist is also a first-line therapeutic option. (For ER+ men in England, NICE guidelines recommend tamoxifen (Nolvadex) as first-line therapy). **From:** ***https://pathways.nice.org.uk/pathways/advanced-breast-cancer#path=view%3A/pathways/advanced-breast-cancer/managing-advanced-breast-cancer.xml&content=view-node%3Anodes-hrpos-and-her2neg***

Second-Line Hormonal and Targeted Treatment Options for Male Hormone Receptor-Positive, HER2- Patients in the US depend upon what endocrine therapy has previously been taken:.

- Possibly any of the above therapies.
- **Alpelisib (Piqray)** in combination with **fulvestrant (Faslodex)** and an LHRH agonist if the cancer has a *PI3K* mutation and you have received at least one prior endocrine-based therapy.
- **Talazoparib (Talzenna) or olaparib (Lynparza)** if you have a germline (inherited) *BRCA1* or *BRCA2* mutation and have had at least one prior chemotherapy.

- **Fam-trastuzumab deruxtecan-nxki (T-DXd; Enhertu)** if your cancer's HER2 expression is either +1, or +2 with negative results on in situ hybridization and you have received at least one prior chemotherapy.
- With an LHRH agonist, **everolimus (Afinitor)** can be taken in combination with either **exemestane** (**Aromasin), fulvestrant (Faslodex), or tamoxifen (Nolvadex),** and one study showed that it conferred a median progression-free survival of 5.9 months for patients who had previously taken a CDK4/6 inhibitor.
- **Third- and Later-Line Hormonal and Targeted Treatment Options for Male Hormone Receptor-Positive, HER2- Patients in the US depend upon what endocrine therapy has previously been taken:**
- Possibly any of the above therapies (although not all options are widely used in a third- or later-line setting).
- **Abemaciclib (Verzenio)** alone (after disease progression on endocrine therapy and prior chemotherapy for MBC).
- Either **Ethinyl Estradiol, megestrol acetate (Megace), or fluoxymesterone (Halotestin).**

Chemotherapy is usually prescribed after 2 to 3 lines of endocrine-based therapies (and/or the targeted therapies above) have stopped working. A clinical trial may also be a consideration. Once the cancer has regressed or stabilized, it may be possible to go back on a previous therapy if sufficient time has elapsed and if the initial response to the therapy had been favorable.

OTHER CONSIDERATIONS

If a man's metastasis is in the **bones**, he should also receive **denosumab** (**Xgeva), zoledronic acid (Zometa), or palmidronic acid (Aredia)** (in addition to his other systemic therapy).

Alpelisib (Piqray) is an oral PI3K inhibitor that was FDA-approved in May 2019 (and by the EU in July 2020) in combination with **fulvestrant (Faslodex)** for the treatment of men (and postmenopausal women) with HR-positive, HER2-, *PIK3CA*-mutated, advanced or metastatic breast cancer following progression on or after an endocrine-based regimen. A diagnostic test called "Therascreen PI3KCA RGQ PCR Kit" has been FDA-approved to detect the mutation in a tissue and/or a liquid biopsy. Detailed information about alpelisib (Piqray) is located under *"Approved Therapies Based Upon Tumor Characteristics."*

It should be noted that for HER2- MBC patients in the US with *BRCA* germline mutations, **talazoparib (Talzenna) and olaparib (Lynparza) have been approved.** (Information about these targeted drugs is located under *"Approved Therapies for Patients with* BRCA *Mutations."*) In Europe, **talazoparib (Talzenna) and olaparib (Lynparza)** have been approved for HER2- MBC patients with *BRCA* mutations who were previously treated with an anthracycline and/or a taxane, or who have progressed after being treated with endocrine therapy or are considered unsuitable for endocrine therapy. **From:** ***https://www.onclive.com/web-exclusives/olaparib-approved-in-europe-for-brca-positive-breast-cancer*** and ***https://www.medscape.com/viewarticle/914777***

If a US patient's cancer has microsatellite instability-high (MSI-H), mismatch repair deficient (dMMR) characteristics (which are very rare), or is tumor mutational burden-high (TMB-H), and if the patient has progressed on prior therapy and has no satisfactory treatment options, **pembrolizumab (Keytruda;** (a PD-1 inhibitor), is an FDA-approved option. This therapy was also approved for patients with unresectable or metastatic TMB-H solid tumors. **Dostarlimab-gxly (Jemperli)** has also been FDA-approved for the treatment of adult patients with dMMR recurrent or advanced solid tumors, as determined by an FDA-approved test, who have progressed on or following previous treatment and who have no satisfactory alternative options.

If a US patient's cancer has a neurotrophic receptor tyrosine kinase (*NTRK*) gene fusion without a known acquired resistance mutation, and if there has been progression on prior therapy with no satisfactory treatment options, **larotrectinib (Vitrakvi)** and **entrectinib (Rozlytrek)** - oral tyrosine kinase inhibitors that act as an "on" or "off" switch in many cellular functions – are FDA-approved options. *NTRK* fusions are extremely rare, occurring in only about 0.5–1% of common cancers. Additional information is contained in the chapter, *"Approved Therapies Based Upon Tumor Characteristics."*

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 receptor-positive breast cancers, 50% of HER2+ breast cancers, and 25% of triple-negative breast cancers (TNBC) are AR positive, making

ARs a possible target for many breast cancers. Furthermore, most male breast cancers are positive for AR. **From[59, PMID:28062545]**
More information about AR therapies can be found in the section entitled, "*Research and Potentially Helpful Therapies."*

Similar to potentially targeting ARs, *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 receptor-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 and other targets can be found in the section entitled, "*Research and Potentially Helpful Therapies*."

12. Approved Therapies for Patients with *BRCA* Mutations

As of July 2019, two drugs **(talazoparib (Talzenna) and olaparib (Lynparza))**, which are **PARP inhibitors**, have been approved for the treatment of HER2- MBC patients who have inherited ("germline") *BRCA* mutations.

PARP is a critical enzyme involved in DNA repair and many other cellular processes. PARP inhibitors are used to treat cancers that have mistakes in their DNA repair genes (also called "tumor suppressor genes"), such as a *BRCA* mutation. When a DNA repair gene is faulty, it cannot successfully repair the damage to DNA that can occur naturally when cells divide.

In cancers where a tumor suppressor gene such as *BRCA* is faulty, the cancer cells are repaired only by a protein called PARP, and the repair is therefore incomplete. This means the cancer cells' DNA is repaired only to a point where they have only a small amount of damage, and therefore the cells are still able to grow and divide. (If the PARP did not repair the DNA, the cancer cells' DNA would have so much damage that the cells would kill themselves and die). So PARP inhibitors act to stop the cancer cells' DNA from being repaired by PARP, allowing the damaged DNA to stay at the critical level that causes the cell to trigger its own death, thus inhibiting the growth of the tumor.

For HER2- MBC patients in the US with *BRCA* germline mutations, **talazoparib (Talzenna) and olaparib (Lynparza)** have been approved. (Information about these targeted drugs is located under *Research and Potential Therapies for Patients with* BRCA1 *and/or* BRCA2 *Mutations*). In Europe, **talazoparib (Talzenna) and olaparib (Lynparza)** have been approved for HER2- MBC patients with *BRCA* mutations who were previously treated with an anthracycline and/or a taxane, or who have progressed after being treated with endocrine therapy or are considered unsuitable for endocrine therapy. **From:** ***https://www.onclive.com/web-exclusives/olaparib-approved-in-europe-for-brca-positive-breast-cancer*** and ***https://www.medscape.com/viewarticle/914777***

Olaparib (Lynparza) is an oral polymerase (PARP) inhibitor that has **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- MBC patients with germline *BRCA* mutations who had received no more than 2 prior chemotherapy regimens, **olaparib (Lynparza)** was compared with a single-agent therapy of the physician's choice. Median progression-free survival was significantly longer in the **olaparib (Lynparza)** group than in the standard-therapy group (7.0 months vs. 4.2 months); and the response rate was 59.9% in the **olaparib (Lynparza)** group and 28.8% in the standard-therapy group. However, the overall survival difference was minimal, at 19.3 months in the **olaparib (Lynparza)** arm versus 17.1 months in the chemotherapy arm. **From[54, PMID:28578601]:** ***https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm592357.htm*** and ***https://www.onclive.com/conference-coverage/sabcs-2019/extended-followup-shows-continued-olaparib-benefit-in-brca-mbc***

Talazoparib (Talzenna) is an oral PARP inhibitor that is used to treat patients with deleterious or suspected deleterious germline *BRCA*-mutant, HER2- locally advanced or metastatic breast cancer. The approval is based on the Phase 3 EMBRACA trial of 431 patients with HER2-, germline *BRCA*-mutant locally advanced or metastatic breast cancer. The patients were randomized to receive either **talazoparib (Talzenna)** or physician's choice of chemotherapy – **capecitabine (Xeloda), eribulin (Haloven), gemcitabine (Gemzar), or vinorelbine (Navelbine)**. Progression-free survival in the **talazoparib (Talzenna)** arm was 8.6 months compared to 5.6 months in the chemotherapy arm. However, **talazoparib (Talzenna)** did not demonstrate a statistically significant overall survival over chemotherapy, although **talazoparib (Talzenna)** improved patient-reported quality of life. Patient feedback revealed a prolonged time until deterioration of overall health at 26.3 months in the **talazoparib (Talzenna)** arm compared to 6.7 months for the chemotherapy arm. (Patient selection for treatment with **talazoparib (Talzenna)** must be based on an FDA-approved companion diagnostic, BRACAnalysis CDx test). **From:** ***https://www.curetoday.com/articles/fda-approves-talzenna-for-breast-cancer-treatment*** and ***https://www.onclive.com/web-exclusives/fda-approves-talazoparib-for-brcamutated-her2negative-breast-cancer*** and ***https://www.eurekalert.org/pub_releases/2020-04/uotm-sfn042420.php***

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.

CLASSES OF APPROVED DRUGS BASED UPON TUMOR CHARACTERISTICS

- **PI3K Inhibitors:** The "phosphoinositide 3-kinase" (PI3K) signaling pathway controls a wide variety of cellular processes, including cell death and survival, cell migration, protein synthesis, and metabolism. When there is a *PIK3CA* mutation, there is corresponding activation of the PI3K pathway, which leads to cancer progression and resistance to endocrine therapy.

- **Monoclonal Antibodies:** Antibodies are an integral part of the body's immune system. Normally the body creates antibodies in response to an "antigen" (a germ that has entered the body, or a specific protein). Antigens are molecules capable of stimulating an immune response, and each antigen has distinct surface features that result in specific responses. Antibodies attach to the antigen in order to mark it for destruction by the immune system. When given to a patient, specific antibodies will attach to matching antigens in much the same way that a key fits a lock. Monoclonal antibodies are laboratory-produced molecules that serve as substitute antibodies that can restore, enhance or mimic the immune system's attack on cancer cells. They are designed to bind to antigens that are generally more numerous on the surface of cancer cells than healthy cells.

  PD-1/PD-L1 Inhibitors are a type of monoclonal antibody. PD-1 is a "checkpoint protein" on specific immune cells called T cells. It normally acts as a type of "off switch" that helps keep T cells from attacking other cells in the body. It does this when it attaches to PD-L1, a protein on some normal (and cancer) cells. When PD-1 binds to PD-L1, it basically tells the T cell to leave the other cell alone. Some cancer cells have large amounts of PD-L1,

which helps them evade immune attack. Monoclonal antibodies that target either PD-1 or PD-L1 can block this binding, therefore boosting the immune system's response against cancer cells.

- **Tropomyosin receptor kinase (Trk) Inhibitors:** Trk is a family of proteins that are found on nerve cells. They are involved in cell signaling pathways that control cell growth, cell maturation, and cell survival. The genes (such as *NTRK*) that make the Trk proteins may have mutations that cause abnormal amounts of the protein to be made, which can cause cancer cells to grow. Trk inhibitors are drugs that can suppress these Trk proteins.

Approved Drugs Based upon Tumor Characteristics

- **Alpelisib (Piqray)**
- **Atezolizumab (Tecentriq)** (no longer available in the US, but still available in Europe)
- **Capivasertib (Truqap)**
- **Dostarlimab-gxly (Jemperli)**
- **Elacestrant (Orserdu)**
- **Entrectinib (Rozlytrek)**
- **Larotrectinib (Vitrakvi)**
- **Pembrolizumab (Keytruda)**

- **Alpelisib (Piqray), a PI3K Inhibitor: Alpelisib (Piqray)** is an oral PI3K inhibitor that was FDA-approved in May 2019 (and by the EU in July 2020) in combination with **fulvestrant (Faslodex)** for the treatment of postmenopausal women (and men) with HR-positive, HER2-, *PIK3CA*-mutated, advanced or metastatic breast cancer following progression on or after an endocrine-based regimen. More recently it was approved by the European Union in July 2020. Approval was based upon the SOLAR-1 Phase 3 clinical trial, which compared **fulvestrant (Faslodex)** plus **alpelisib (Piqray)** versus **fulvestrant (Faslodex)** and placebo in postmenopausal patients with *PIK3CA* mutations. Patients in the **fulvestrant (Faslodex)/alpelisib (Piqray)** arm fared substantially better (median progression-free survival (PFS) 11.0 months) than similar patients in the **fulvestrant (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 overall response rate in the *PIK3CA*-mutant cohort was 26.6% in the **fulvestrant (Faslodex)/alpelisib (Piqray)** arm compared with 12.8% in the **fulvestrant (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 the **fulvestrant (Faslodex)/alpelisib (Piqray)** arm. (There was no advantage to providing alpelisib (Piqray) in patients without a *PIK3CA* mutation). The FDA has approved the companion diagnostic test "Therascreen PIK3CA RGQ PCR Kit" to detect the *PIK3CA* mutation in a tissue and/or a liquid biopsy, as well as the FoundationOne CDx test. It should be noted that patients treated with **alpelisib (Piqray)** have experienced severe hyperglycemia (high level of glucose in the bloodstream), and the safety of **alpelisib (Piqray)** in those with type 1 or uncontrolled type 2 diabetes is not known. Therefore, the FDA advises that patients on alpelisib (Piqray) obtain fasting glucose and HbA1C levels, and be monitored (and treated if/as necessary) for glycemic control. **From:** ***https://www.targetedonc.com/news/alpelisib-receives-fda-approval-in-breast-cancer*** and ***https://www.fda.gov/news-events/press-announcements/fda-approves-first-pi3k-inhibitor-breast-cancer*** and ***https://www.targetedonc.com/publications/targeted-therapy-news/2019/October-2019/patient-with-a-pik3capositive-tumors-exhibits-hyperglycemia-associated-with-alpelisib*** and ***https://www.oncnet.com/news/fda-approves-companion-diagnostic-alpelisib-pik3ca-mutated-breast-cancer***

The **fulvestrant (Faslodex)/alpelisib (Piqray)** combination boosted overall survival (OS) by 8 months over **fulvestrant (Faslodex)** alone (reported to be too small a difference to reach statistical significance). However, for patients with lung or liver metastases, OS improved by more than 14 months to a median of 37.2 months. Furthermore, patients in the trial taking the **fulvestrant (Faslodex)/alpelisib (Piqray)** combination were able to delay chemotherapy by a median time of 23.3 months, versus 14.8 months for the patients taking **fulvestrant (Faslodex)** alone. **From:** ***https://www.fiercepharma.com/pharma/esmo-novartis-posts-long-awaited-survival-data-for-breast-cancer-blockbuster-hopeful-piqray***

- **Atezolizumab (Tecentriq) with paclitaxel (Abraxane). Atezolizumab (Tecentriq) is a PD-1 inhibitor** administered intravenously that initially appeared to work well in combination with **paclitaxel (Abraxane)** as first-line treatment for TNBC MBC

patients whose tumors express PD-L1. **Atezolizumab (Tecentriq)** was studied in the IMPassion130 trial, which determined that MBC patients whose tumors expressed PD-L1 had a median overall survival of 25.0 months in those taking **atezolizumab (Tecentriq)** with **paclitaxel (Abraxane)** vs. 18.0 months for those taking **paclitaxel (Abraxane)** alone, and the respective 24-month overall survival rates were 51% and 37%. In March 2019, the FDA granted accelerated approval to **atezolizumab (Tecentriq)** in combination with **paclitaxel (Abraxane)** as initial treatment for TNBC patients in the US with unresectable locally advanced or metastatic disease whose tumors express PD-L1 (PD-L1 stained tumor-infiltrating immune cells of any intensity covering ≥1% of the tumor area). However, in Aug. 2021 this combination was taken off market in the US, but it is still available in Europe.
From:
https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm633065.htm and
https://www.medscape.com/viewarticle/914068#vp_2 and
https://www.medpagetoday.com/hematologyoncology/breastcancer/94243?fbclid=IwAR24OVkLy_ItKwffSMcI7WoOEE6rswiIazOJ8BfwtKWQV_13NwZW9od1FzY&vpass=1

- **Capivasterib (Truqap).** In November 2023, the FDA approved capivasertib (Truqap) plus fulvestrant (Faslodex) as second-line treatment for HR+, HER2- MBC with alterations in the genes *PIK3CA*, *AKT1*, and/or *PTEN*. These alterations can be detected with an FDA-approved companion diagnostic test. From: ***https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-capivasertib-fulvestrant-breast-cancer***

- **Dostarlimab-gxly (Jemperli),** a PD-1 Inhibitor: **Dostarlimab-gxly (Jemperli)** is a PD-1 inhibitor targeted therapy administered intravenously that has been approved for patients with metastatic mismatch repair deficient (dMMR) solid tumors (as determined by an FDA-approved test) that have progressed following prior treatment and who have no satisfactory alternative treatment options. Findings of the GARNET trial indicated that the agent elicited an objective response rate (ORR) of 41.6% in all dMMR solid tumors. The median duration of response (DOR) was 34.7 months (range 2.6-35.8+) with 95.4% of patients experiencing a response that persisted for 6 months or longer. **From:** ***https://www.onclive.com/view/fda-approves-dostarlimab-gxly-for-dmmr-recurrent-or-advanced-solid-tumors?fbclid=IwAR3nRWYz***

BgGMq3xk6MIfgs9LKxWMuW6i87JUA4qMDGK9xh95zhFmhpkr-Qg

- **Elacestrant(Orserdu).** In January 2023, the FDA approved elacestrant (Orserdu), the first oral SERD, as second-line treatment for postmenopausal women or men with ER+, HER2- MBC with a mutation in the gene for the estrogen receptor, called ESR1. This mutation can be detected with an FDA-approved companion diagnostic test. From: ***https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-elacestrant-er-positive-her2-negative-esr1-mutated-advanced-or-metastatic-breast-cancer***

- **Entrectinib (Rozlytrek)**: In a manner similar to **larotrectinib (Vitrakvi),** above, **entrectinib (Rozlytrek)** was FDA-approved in Aug. 2019 for the treatment of individuals with cancers that harbor a *NTRK* gene fusion and for whom there are no effective treatments. Data from four clinical trials of 54 patients with *NTRK* fusion-positive tumors, which included cancers of the lung, salivary gland, breast, thyroid and colon/rectum, showed an overall response rate of 57%, with 7.4% of patients achieving complete response. 61% of the 31 patients with tumor shrinkage had responses lasting for at least 9 months, and objective responses to **entrectinib (Rozlytrek)** were also seen in patients with central nervous system metastases at baseline. **From:** ***https://www.healio.com/hematology-oncology/lung-cancer/news/online/%7B04b7e14d-21f5-4bb3-bbc3-47263789349f%7D/fda-approves-rozlytrek-for-cancers-with-ntrk-gene-fusion-ros1--positive-non-small-cell-lung-cancer***

- **Larotrectinib (Vitrakvi), a Trk Inhibitor:** In Nov. 2018, the FDA granted an accelerated approval to the oral drug **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. *NTRK* fusions are rare in most cancers, occurring in around 0.5–1% of common cancers. **Larotrectinib (Vitrakvi)** is an oral tyrosine kinase inhibitor (an enzyme that acts as an "on" or "off" switch in many cellular functions), which was approved based upon findings from patients with TRK-positive tumors who were enrolled across 3 clinical

trials. In results published in the *New England Journal of Medicine* (NEJM), **larotrectinib (Vitrakvi)** 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). There are several genomic tests available to detect the *NTRK* gene fusion, and interested patients may wish to discuss this type of testing with their medical oncologist.

At 1 year on **larotrectinib (Vitrakvi),** 71% of responses were ongoing, with more than half (55%) of patients remaining progression free. 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:** ***https://www.onclive.com/web-exclusives/fda-approves-larotrectinib-for-ntrk-cancers***

- **Pembrolizumab (Keytruda)**, a PD-1 Inhibitor*:* ***Pembrolizumab (*Keytruda)** is a PD-1 inhibitor targeted therapy administered intravenously that has been approved for patients with metastatic, microsatellite instability-high (MSI-H), mismatch repair deficient (dMMR), or tumor mutational burden-high (TMB-H) 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 **pembrolizumab (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%). 78% of responding patients had responses that lasted for 6 months or longer. **From:** ***https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm560040.htm***

  An option for TNBC MBC patients whose tumors are PD-L1 positive is the combination of **pembrolizumab (Keytruda)** and chemotherapy. This combination was based upon the KEYNOTE-355 trial, which randomized TNBC MBC patients who had not previously taken chemotherapy in the metastatic

setting to receive either **pembrolizumab (Keytruda)** plus chemotherapy or chemotherapy alone. The median progression-free survival was 9.7 months for patients taking the combination vs. 5.6 months for patients taking chemotherapy only. A test called PD-L1 IHC 22C3 pharmDx has been FDA-approved as a companion diagnostic for selecting patients with TNBC to be eligible for the **pembrolizumab (Keytruda)** plus chemotherapy regimen. **From:** ***https://www.fda.gov/drugs/drug-approvals-and-databases/fda-grants-accelerated-approval-pembrolizumab-locally-recurrent-unresectable-or-metastatic-triple***

In 2020, **pembrolizumab (Keytruda)** was approved for patients with unresectable or metastatic tumor mutational burden-high (TMB-H) solid tumors, which are tumors having 10 or more mutations per megabase (a length of genomic segment). Approval was based on an analysis of 102 patients with various cancer types that were TMB-H. 30 patients (29%) experienced a response to treatment, including 4% with a complete response and 25% with a partial response. In addition, 57% of patients who experienced a response to treatment had ongoing responses of 12 months or longer, and 50% had ongoing responses of 24 months or longer. The FDA has approved the FoundationOne® CDx test as the companion diagnostic to identify patients with solid tumors that are TMB-H who may benefit from treatment with **pembrolizumab (Keytruda)** alone. **From:** ***https://www.curetoday.com/articles/fda-approves-keytruda-to-treat-tumor-mutational-burdenhigh-solid-tumors-#:~:text=FDA%20Approves%20Keytruda%20to%20Treat%20Tumor%20Mutational%20Burden%2DHigh%20Solid,cancer%20types%2C%20including%20rare%20cancers.***

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 **trastuzumab-Dkst (Ogivri)** as a biosimilar to **trastuzumab (Herceptin)** for the treatment of patients with metastatic breast or metastatic stomach cancer whose tumors overexpress the HER2 gene (HER2+). **Trastuzumab (Ogivri),** which is administered intravenously, 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 **trastuzumab-pkrb (Herzuma),** which is administered intravenously, as a biosimilar to **trastuzumab (Herceptin)** for patients with HER2-overexpressing MBC, either in combination with paclitaxel (Abraxane) 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 **trastuzumab-dttb (SB3; (Ontruzant),** a biosimilar to **trastuzumab (Herceptin),** for the treatment of patients with HER2-overexpressing breast cancer (including MBC) or metastatic gastric or gastroesophageal junction adenocarcinoma. It is administered intravenously. **From:** ***https://www.targetedonc.com/news/third-trastuzumab-biosimilar-gains-fda-approval***

- In March 2019, the FDA approved a **trastuzumab (Herceptin)** biosimilar called **trastuzumab-qyyp (Trazimera),** which had been approved in Europe in 2018 (below). It is administered intravenously. **From:** ***https://www.healio.com/hematology-oncology/breast-cancer/news/online/%7B202349ef-5342-4f78-a22f-1b87beda4623%7D/fda-approves-trazimera-herceptin-biosimilar-for-certain-breast-gastric-cancers***

- In June 2019, the FDA approved **trastuzumab-anns (Kanjinti)** for the treatment of HER2-overexpressing breast cancer, which is the fifth biosimilar to **trastuzumab (Herceptin)** to receive FDA approval. It is administered intravenously. **From:** ***https://www.pharmalive.com/fda-approves-amgen-and-allergans-kanjinti/***

In Europe:

In Aug. 2018, the European Union approved the intravenous drug **Trazimera**, a biosimilar to **trastuzumab (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 and overall survival were similar between the treatment groups. **From:** ***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.

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 1-10% 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 5 cm. 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 who had a single organ or 2 organs involved. In those cases where effects of systemic therapy, possibly in combination with other treatments, were evaluated, a CR or 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 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 probability for clinical cure. **From[65, PMID:22532161]:** ***http://www.ncbi.nlm.nih.gov/pubmed/22532161***.

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 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:** ***https://www.eurekalert.org/pub_releases/2018-10/asfr-hrt101618.php***

Despite the encouraging study results depicted above, the outcome disclosed in 2022 of the NRD-BR002 study, which compared standard of care (SOC) therapy with SOC + SBRT for 125 newly diagnosed patients with oligometastatic disease (≤4 extracranial mets and controlled primary disease), painted a completely different picture. The study randomized 65 patients into Arm 1 for SOC treatment, and 60 patients into Arm 2 for treatment with SOC + SBRT. 79% of the patients had ER+ or PR+/HER2- disease, 13% were HER2+, and 8% triple negative. 60% had 1 metastasis and 20% presented synchronously with primary disease. The median follow-up was 30 months, and it was found that the median PFS for patients in Arm 1 was 23 months and for patients in Arm 2 it was 19.5 months. OS at 36 months was similar in both groups: for patients in Arm 1 it was 71.8% and for patients in Arm 2 it was 68.9%. **From:** ***https://ascopubs.org/doi/10.1200/JCO.2022.40.16_suppl.1007***

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[66, 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:** ***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:** ***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 "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[60, 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, 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, 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 composed 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 the 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** (to monitor bone density during treatment)
- **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 3.9–5.03 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 circulating tumor DNA (ctDNA) in the body, as genetic sequencing of ctDNA 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[61, PMID:27532364]:** ***http://www.eurekalert.org/pub_releases/2015-12/mskc-msh121115.php***

ctDNA testing is performed with a blood test and is used to identify mutations in genes for which a drug is available that targets that mutant form of the protein resulting from the mutated gene. Other mutations can be detected even if an FDA-approved companion diagnostic and targeted therapy are not available or are only available in clinical trials. The FDA has a searchable table listing approvals that have a companion diagnostic: ***https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools.*** We searched the above for "breast" and then limited the result to plasma or whole blood.

Diagnostic Name (Manufacturer)	**Indication - Sample Type**	**Drug Trade Name (Generic) NDA / BLA**	**Biomarker(s)**
FoundationOne Liquid CDx (Foundation Medicine, Inc.)	Breast Cancer - Plasma	alpelisib (Piqray) NDA 212526	*PIK3CA*
Guardant360 CDx (Guardant Health, Inc.)	Breast Cancer - Plasma	elacestrant (Orserdu) NDA 217639	*ESR1*
therascreen PIK3CA RGQ PCR Kit (QIAGEN GmbH)	Breast Cancer - Tissue or Plasma	alpelisib (Piqray) NDA 212526	*PIK3CA*
BRACAnalysis CDx (Myriad Genetic Laboratories, Inc.)	Breast Cancer - Whole Blood	olaparib (Lynparza) NDA 208558	*BRCA1* or *BRCA2*

BRACAnalysis CDx (Myriad Genetic Laboratories, Inc.)	Breast Cancer - Whole Blood	talazoparib (Talzenna) NDA 211651	*BRCA1* or *BRCA2*
FoundationOne® CDx	Breast Cancer-	capivasertib (Truqap)	*PIK3CA*, *AKT1*, or *PTEN*

In addition to the GuardantCDx shown in the above table, another test they offer to determine response to treatment is the Guardant 360 Response:
https://guardanthealth.com/products/tests-for-patients-with-advanced-cancer/

- **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 20-120 U/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 0.2-1.2 mg/dL
  Lactate dehydrogenase (LDH) Normal levels are 100-220 U/L
  This information is **From:** ***https://chemocare.com/sideeffect/liver-problems***

- **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[63, PMID:26195705]**

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 into 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.

- **A 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[64, PMID:15317891]**

- **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 passes 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 that is used in **FDG PET** scans. 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. Another type of PET scan is **FES PET**, which uses a radiotracer composed of estrogen that emits radiation and highlights estrogen receptor (ER)-positive cancer cells to determine whether a lesion may respond, or is responding, to endocrine therapy. This test may be especially useful in detecting ER+ lesions that may respond to endocrine

therapy in patients with difficult-to-identify lobular cancer and/or brain metastases.

- **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/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 indicate 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[67, 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 and 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[2, PMID:17557947; 68, PMID:26167483]:** ***https://www.ncbi.nlm.nih.gov/pubmed/17557947*** and ***http://www.medicalnewstoday.com/releases/286501.php***

The seed and soil hypothesis states that the cancer cell, which is the "seed" will only grow if it is in the right "soil". Metastasis can start out as single cells or small clumps of cells, and if the environment around it is right, it can grow. If the environment is wrong for the cancer cell, then it can't grow. The environment for that cancer cell is different depending on the site of metastasis, e.g., bone or liver etc., as well as the overall environment of the body it is growing in. That's where

things like exercise and smoking mentioned above come in. These things can affect the environment of the cancer cells and tumors.

An important part of the microenvironment is the immune system. The immune system's job is to protect you from germs as well as cancer cells. It does this through the use of white blood cells and lots of signaling molecules. It's also a double-edged sword, because if it is overactive, it can lead to things like allergic reactions or autoimmune disorders. However, if it's underactive, then we are immunocompromised and germs can make us sick or kill us, as can cancerous cells. The microenvironment of the tumor may contain a lot of immune cells that the cancer cells can trick into leaving them alone or even lead to increased growth of cancerous cells.

Beyond the microenvironment, the status of the immune system as a whole can affect tumor growth.

Each human is an entire ecosystem of human cells as well as bacterial and fungal cells and viruses, called the microbiome. These are important to our ability to digest food, and some bacteria produce vitamins for us to absorb and use. But scientists are finding out that these microbes, particularly bacteria as they have been most studied, are involved in many more body processes, including cancer development and control. For example, there are bacteria that can affect the amount of estrogen in the blood, which is an important factor for hormone receptor-positive cancers. Additionally, there is evidence that the microbiome plays a role in the immunotherapy response. We also know that tumors, including breast primaries and metastasis, can have bacteria inside them. However, scientists don't know yet what this means for controlling tumor growth and spread, and research is ongoing. If you are considering probiotics, it's important to speak with your doctor.

https://pubmed.ncbi.nlm.nih.gov/31847455/ and
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8247384/

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

People diagnosed with MBC are encouraged to determine whether they carry an inherited (germline) mutation, and if warranted, to also undergo testing for tumor-related (somatic) mutations.

As tests regarding genetic alterations become more widely used, patients should be aware that the **Nondiscrimination Act (GINA) of 2008** protects Americans from discrimination based on their genetic information with regard to health insurance and employment.

In Feb. 2019, **the American Society of Breast Surgeons recommended that all patients with breast cancer should be offered genetic testing** that includes ***BRCA1*, *BRCA2*,** and ***PALB2***. It is noteworthy that these recommendations also indicate that patients with previous genetic testing may benefit from updated testing, since genetic testing done before 2014 likely did not test for *PALB2* or other relevant mutations.

From:

https://www.healio.com/hematology-oncology/breast-cancer/news/online/%7B0893790b-c290-4344-9c7b-08d3a2343f57%7D/american-society-of-breast-surgeons-recommends-genetic-testing-for-all-patients-with-breast-cancer

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, and treatments exist for many of these. Currently, clinical trials are underway to determine which mutation-based therapies may work best for a given mutation.

Approaches to personalized medicine

A biomarker is a substance in your body that can be measured and that can give information about your health. In cancer, biomarker testing is the "umbrella" term used to describe molecular testing or genomic testing. Biomarker testing can be performed on a tissue biopsy of a tumor or tumor cells or on molecules (like DNA) found in blood (called

circulating tumor DNA [ctDNA]) or other biological fluids. Tests that look at DNA include genomic testing for tumor mutations.

Important biomarkers in MBC include the estrogen and progesterone receptors and HER2. Other biomarkers are listed in the table below.

Biomarker testing is important because many times, the results will help your healthcare team recommend appropriate treatment options for you and may open up more clinical trial options.

Class of Biomarker	**Examples**	**Type(s) of Testing**	**Practical Uses**	**Companies**
Receptors	Estrogen Receptor Progesterone Receptor HER2	Immunohistochemistry (IHC) from a tissue biopsy or liquid biopsy (pleural effusion, ascites and/or cerebrospinal fluid)	Help inform treatment decisions	N/A This is usually done at the hospital in their own pathology lab
Genomic Mutations (Tumor Mutations)	**Mutations in the following genes (not an exhaustive list):** *ESR1*, *PIK3CA*, *PTEN*, *AKT* **Other genomic alterations:** Microsatellite Instability (MSI high or not); Mismatch Repair Status (MMR	Genomic testing for somatic/tumor mutations from a tissue biopsy **or** a blood test for ctDNA (sometimes also called a "liquid biopsy") Note: genomic mutations in the tumor can change over time so it's important to have more than	Help inform treatment decisions	For tissue: Caris, Foundation One CDX For ctDNA (liquid /blood biopsy): Guardant 360 CDx, Foundation One Liquid CDx

	proficient or deficient); Tumor Mutational Burden (TMB; high or not)	one test, especially at progression		
Other	PD-L1, Ki-67, androgen receptor	Immunohistochemistry (IHC) from a tissue biopsy or liquid (pleural effusion, ascites and/or cerebrospinal fluid) biopsy	PD-L1 to inform treatment decisions. Ki-67 is a measure of how quickly cancer cells are dividing (over 30% is high)	N/A This is usually done at the hospital in their own pathology lab
Tumor Markers	CA 27-29, CA 15-3, CEA	Blood test	Can be useful in some cases to track progression in combination with imaging and symptoms	N/A This is usually done at the hospital in their own lab

The flow chart in this link may help you discuss your need for biomarker testing with your doctor: ***https://www.lungevity.org/biomarkerdiscussionguide***

Biomarkers can be found in blood samples, as shown in the below table, which was derived from: ***https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-***

or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools

The below table contains specific blood tests used to match mutations with treatments. The biomarker column lists the gene in which the mutation is found. The table was created by searching the FDA table in the above link for "breast" and then limiting the results to plasma or whole blood.

Diagnostic Name (Manufacturer)	**Indication - Sample Type**	**Drug Trade Name (Generic) NDA / BLA**	**Biomarker(s)**
FoundationOne Liquid CDx (Foundation Medicine, Inc.)	Breast Cancer - Plasma	alpelisib (Piqray) NDA 212526	*PIK3CA*
Guardant360 CDx (Guardant Health, Inc.)	Breast Cancer - Plasma	elacestrant (Orserdu) NDA 217639	*ESR1*
therascreen PIK3CA RGQ PCR Kit (QIAGEN GmbH)	Breast Cancer - Tissue or Plasma	alpelisib (Piqray) NDA 212526	*PIK3CA*
BRACAnalysis CDx (Myriad Genetic Laboratories, Inc.)	Breast Cancer - Whole Blood	olaparib (Lynparza) NDA 208558	*BRCA1* or *BRCA2*
BRACAnalysis CDx (Myriad Genetic Laboratories, Inc.)	Breast Cancer - Whole Blood	talazoparib (Talzenna) NDA 211651	*BRCA1* or *BRCA2*
FoundationOne®CDx	Breast Cancer-	capivasertib (Truqap)	*PIK3CA*, *AKT1*, or *PTEN*

- **"Germline" or genetic testing for inherited mutations using blood or saliva** can determine whether the patient has a familial mutation, such as *BRCA1*, *BRCA2*, and/or *PALB2*. As previously

mentioned, HER2- MBC patients with *BRCA* mutations are eligible for treatment with drugs called "PARP Inhibitors" (**olaparib (Lynparza) or talazoparib (Talzenna)),** which are also being tested with encouraging results on MBC patients with *PALB2* mutations.

Type of Test	**Examples**	**Type(s) of Testing**	**Practical Uses**	**Companies**
Genetic testing for inherited mutations	Mutations in the following genes (not an exhaustive list): *BRCA1*, *BRCA2*, *CHEK2*, *PALB* etc.	Genetic testing for inherited mutations can be from a blood or saliva (spit) sample Note: any genetic mutation you have will not change over time; however, you may consider additional testing if the first test you had didn't cover many genes (current tests have dozens plus). Also, consulting with a genetic counselor is recommended.	Determine treatment as in a *BRCA* mutation and/or inform self and family members about cancer risk (not limited to breast cancer)	Invitae

- **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, 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.

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[69]:** ***http://meetinglibrary.asco.org/content/118466-132***

The **Weisenthal Cancer Group** conducts chemo sensitivity testing (***http://www.weisenthalcancer.com/***; Dr. Weisenthal mentored Dr. Nagourney, who leads RT).

- **Integrative Care:** 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 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 the mainstream cancer therapy prescribed by their medical oncologist. Among naturopathic oncologists, those who carry the title "FABNO" (Fellow by the American Board of Naturopathic Oncology) have

passed special examinations for meeting the highest standard of the profession.

That said, not all FABNOs are alike, any more than all medical oncologists 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 intended to complement the conventional treatment provided by the patient's medical oncologist.

It may be possible to work remotely via phone, email, Zoom, 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://www.oncanp.org/find-an-nd#!directory/map***

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. Patient-Centered Dosing

If you are undergoing treatment for your cancer, it's likely that you've experienced side effects from your therapy. In fact, a survey of 1,221 patients with MBC revealed that 86% had at least one bad treatment-related side effect, and of these 20% visited the hospital and 43% missed treatment. These statistics indicate that side effects are very common and may, in some cases, have significant consequences such as the need for acute care. Subsequent chapters in this Guide describe many common side effects and strategies for relieving them.

The reason for the prevalence and severity of patients' side effects is the decades-old oncology drug paradigm that proclaimed "More is Better!" In summary, it was believed that the higher the dose and toxicity, the greater the efficacy.

Therefore, Phase 1 dose escalation clinical trials tend to focus on identifying the "maximum tolerated dose (MTD)" - the highest dose of a treatment that does not cause unacceptable side effects. This dose is often referred to as the "recommended phase 2 dose (RP2D)," which is studied in Phase 2 trials. However, for patients in clinical trials and in the real world, this dose may nevertheless produce considerable side effects.

As can be imagined, there are several limitations regarding Phase 1 dose escalation in that it:

- is based on the premise that higher toxicity implies greater efficacy
- includes a small number of patients (usually 20–30 participants), generally with 3 participants at each dosage level
- does not account for long-term treatment-related side effects
- ignores levels of drug efficacy
- is not entirely relevant for targeted therapies, where clinically significant side effects may not occur at doses above the optimal biological dose (the lowest safe dose associated with biological efficacy)
- does not consider the fact that patients' responses in the "real world" may differ from those of patients in clinical trials because they are not subject to rigid inclusion and exclusion criteria, and because each patient is as unique as their fingerprints

Why do dosage levels matter, especially to individuals with MBC?

Unlike early-stage breast cancer patients, patients with MBC are treatable but not curable, and most will remain on therapy for the rest of their lives. At the beginning of each treatment patients are usually prescribed the "recommended starting dose (RSD)" that's based on the MTD, which may cause the most – and worst – side effects. The consequences are that additional medical care may be needed, scheduled treatments may be missed, a treatment that's working may need to be stopped or switched due to toxicity, and patients may become too ill from cumulative treatments to take full advantage of the therapies approved for their MBC subtype.

Conversely, lower doses may enable patients to remain on a working therapy longer, miss fewer treatments, take fuller advantage of the treatments available to them, and feel better overall.

Although not all drugs for MBC are available in several doses, many are. Typically, lower doses are only prescribed after a patient experiences significant side effects on the RSD. Dose reduction can be very effective in relieving side effects, and according to the aforementioned survey, 83% of the patients given a dose reduction felt better on the lower dose.

Notably, recent evidence suggests that lower doses of some MBC therapies may be as effective as the RSD while causing less severe side effects. ***www.therightdose.org***

The above situation gave rise to the Patient-Centered Dosing Initiative (PCDI), a movement launched in 2019 by MBC patient advocates supported by an advisory board of five medical oncologists (Drs. Aditya Bardia, Mark E. Burkard, Kevin Kalinsky, Maryam Lustberg, and Hope Rugo). At ASCO's 2021 Annual Worldwide Meeting, the PCDI presented a new paradigm: for drugs that are available in multiple doses, instead of prescribing the RSD at the beginning of each new treatment and eventually reducing the dose when the patient experiences side effects, *personalize* the starting dose in clinical practice based upon patient's unique characteristics. This is a logical application of the concept of personalized medicine.

The patient's characteristics that doctors and patients may discuss with regard to dosage include:

1. Personal goals and wishes
2. Performance status (other illnesses, age, etc.)
3. History of side effects from other drugs
4. Current and historical blood count levels
5. Whether the disease is aggressive or indolent
6. Whether there is organ dysfunction or central nervous system metastasis
7. Patient's body mass index

8. Patient's financial situation (*if additional medications or specialists are needed to mitigate side effects, can the patient afford them?)*
9. Availability of the patient's at-home care *(if the side effects are severe, is there anyone available at home to assist?)*

Is it realistic for patients and medical oncologists to collaboratively discuss dosing options and jointly select the optimal dose for the patient? Based upon the results of the PCDI's MBC Patient and Medical Oncologists' Surveys, this is a highly reasonable expectation because:

- more than half (53%) of patients with MBC and 85% of medical oncologists do not believe that a higher dose of a cancer drug is always more effective than a lower dose, and
- 92% of patients and 97% of medical oncologists would be willing to collaboratively discuss flexible MBC drug dosing options based upon the patient's unique personal characteristics

Another consideration pertains to the U.S. Food and Drug Administration's (FDA's) perspective about oncology drug dosages. Notably, five months after the PCDI's presentation at the ASCO 2021 Worldwide meeting, Atik Rahman, Ph.D., FDA Division Director, stated, *"It's loud and clear from our patients that the drugs are too toxic… patients deserve a more tolerable dose."* Furthermore, in an article entitled "The Drug-Dosing Conundrum in Oncology - When Less Is More," published in the Oct. 2021 edition of the *New England Journal of Medicine*, the FDA stated that Phase 1 dose escalation trials should no longer be based upon the MTD paradigm. Instead, they should identify at least two different doses based upon safety and efficacy to be further studied in subsequent clinical trials. **From: *https://ascopost.com/news/october-2021/fda-perspective-on-drug-dosing-in-oncology-from-more-is-better-to-less-can-be-more/***

Hence we are witnessing the birth of a new paradigm regarding oncology drugs: instead of "More is Better," "Optimal is Better."

The PCDI's and the FDA's approaches to drug dosing are complementary because:

The FDA is focusing on *optimizing the dose in clinical trials* so that patients are not subject to unnecessary toxicities

The PCDI is focusing on *personalizing the dose after the drug is approved* and the patient is sitting with the doctor in the clinic. In this regard, patient-centered dosing remains important because:

- approved drugs currently on the market will continue to be prescribed based upon the RSD
- it will take a while for drug development to leverage the new paradigm
- patients' responses in the real-world differ from those of patients in clinical trials because they are not subject to rigid inclusion/exclusion criteria
- patients will always have unique personal attributes (comorbidities, drug sensitivities, etc.)

As a result of the FDA's and PCDI's efforts, patients may:

- need less emergency care
- miss fewer treatments
- potentially remain on a working treatment longer
- take broader advantage of the approved treatments available to them
- experience a better quality of life

Patients are highly encouraged to speak with their medical oncologists about side effect mitigation strategies and are reminded to never change anything about treatment on their own – always speak with the physician first!

The Patient-Centered Dosing Initiative is proud that the results of its 2021 Medical Oncologists Survey about treatment-related side effects and individualized dosing for patients with MBC has been published in the peer-reviewed journal *Breast Cancer Research and Treatment*. The article can be found here: ***https://link.springer.com/epdf/10.1007/s10549-022-06755-5?sharing_token=tcuv5iN1T-Z2RyN6CmDIIve4RwlQNchNByi7wbcMAY5twr2bHFnUaIoI7jqZEtqJIhFkwwCFPSvCEkppLO_kEN716pupeEOxm5G1JDO3VRG9-tkIazXOX6c9sl4FqeC7lvsgR03wH4G1ff_w1Btab9aVtC0zdmsXwJajqjsonIQ%3D***

A table has been developed that outlines dose-reduction suggestions (updated March 2023): ***https://www.therightdose.org/s/Drug-Dosages-Updated-File-March-2023.xlsx***

For additional information about patient-centered dosing, please visit ***https://www.therightdose.org/***

21. 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 or 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.

Supplement Use

An observational study of early-stage (not metastatic) breast cancer patients correlated the use of antioxidants before and during chemotherapy with an increased risk for their breast cancer returning and, to a lesser degree, with an increased risk for death. Antioxidants included Vitamin A, Vitamin C, and Vitamin E, as well as carotenoids and coenzyme Q10. Vitamin B12, iron, and omega-3 fatty acid use was also associated with poorer outcomes. (Multivitamin use was not associated with survival outcomes). Therefore, patients who are considering (or are already) taking supplements are highly encouraged to discuss them with their medical teams. **From:** ***https://www.healio.com/hematology-oncology/breast-cancer/news/onl***

ine/%7B395ec09e-4fb8-434a-8b69-fae07835e102%7D/antioxidant-supplements-linked-to-increased-risk-for-breast-cancer-recurrence-death?page=1

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[71, 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. Analysis of several studies showed that using a beta blocker called **carvedilol (Coreg)**. (Beta blockers slow down the heart and lower blood pressure) can reduce cardiotoxicity and a type of heart damage called ventricular remodeling but not another type of heart problem called LVEF decrease. Another study showed that Coenzyme Q10 (CoQ10) may also afford some heart protection for women undergoing chemotherapy and trastuzumab (Herceptin), which can compromise heart function. **From:** *https://pmc.ncbi.nlm.nih.gov/articles/PMC6476829/* and *https://pmc.ncbi.nlm.nih.gov/articles/PMC10652675/*

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% 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[72, 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 dihydropyrimidine dehydrogenase (DPD) deficiency relative to **capecitabine (Xeloda)** and 5FU mentioned below. 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 capecitabine (Xeloda) or 5-FU: Patients about to go on the chemo drugs **capecitabine (Xeloda)** or 5-FU should first speak with their doctor about getting tested for specific mutations in the (dihydropyrimidine dehydrogenase (*DPD*) gene that could cause severely toxic or potentially life-threatening reactions to these drugs. Approximately 3-5% 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. The FDA recently approved new labeling regarding 5-FU for injection and DPD deficiency**. From:** ***https://www.sciencedirect.com/topics/medicine-and-dentistry/dihydropyrimidine-dehydrogenase-deficiency*** and ***https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-safety-labeling-changes-regarding-dpd-deficiency-fluorouracil-injection-products***

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, and 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/m^2 **doxorubicin (Adriamycin)**/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/m^2. The conclusion was that weekly low-dose **doxorubicin (Adriamycin)** monotherapy showed modest activity and was devoid of severe toxicity in heavily pretreated MBC patients. **From[73, 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, **capecitabine (Xeloda)** might be a viable option. In a study of 78 elderly MBC patients comparing pegylated liposomal doxorubicin or "PLD" (**Doxil**) with **capecitabine (Xeloda),** median progression-free

survival was 5.6 months for the PLD (**Doxil**) group versus 7.7 months for the **capecitabine (Xeloda)** group. Median overall survival was 13.8 months for patients on PLD (**Doxil**) and 16.8 months for those on **capecitabine (Xeloda). From[74, 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 **[75, 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 **denosumab (Xgeva)** to help preserve bone density. In turn, bisphosphonates and **denosumab (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 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 **denosumab (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 (Xeloda)**) 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[76, 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[77, 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 (Doxil)** and **epirubicin (Ellence)** damage and disrupt the creation of DNA

3. **Antimetabolites** such as **capecitabine (Xeloda), fluorouracil, gemcitabine (Gemzar)**, and methotrexate prevent the "building blocks" of DNA from being used.

4. **Microtubule inhibitors** such as **docetaxel (Taxotere), eribulin (Halaven), ixabepilone (Ixempra), paclitaxel (Abraxane), and vinorelbine (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[13, 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***

The National Comprehensive Cancer Network (NCCN) provides guidelines for treatment of people with MBC. The patient version can be found here: ***https://www.nccn.org/patients/guidelines/content/PDF/stage_iv_breast-patient.pdf***. More information is available in the professional guidelines: (***https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf***).

You can create a free account to view the professional guidelines. The information provided below is current as of 2023. Please see the above guidelines for the most recent updates.

In addition, the American Society of Clinical Oncology (ASCO) also provides guidelines.

CHEMOTHERAPY DRUGS FOR MBC BASED UPON NCCN GUIDELINES

Chemotherapy Agents and Combination	
Generic name	**Brand name**
Doxorubicin	**Adriamycin**
Epirubicin	**Ellence**
Liposomal Doxorubicin	**Doxil**
Paclitaxel	**Taxol**
Docetaxel	**Taxotere**
Protein-Bound Paclitaxel (nab-paclitaxel)	**Abraxane**
Capecitabine	**Xeloda**
Gemcitabine	**Gemzar**
Vinorelbine	**Navelbine**
Eribulin	**Halaven**
Cyclophosphamide	**Cytoxan**
Cisplatin	**(various)**
Carboplatin	**(various)**
Fluorouracil (5-FU)	**Adrucil**
Methotrexate	**(various)**
Ixabepilone	**Ixempra**
Often-used combinations:	
Doxorubicin, Cyclophosphamide	**(AC)**
Epirubicin, Cyclophosphamide	**(EC)**
Cyclophosphamide, Methotrexate (Folex), Fluorouracil	**(CMF)**
Docetaxel, Capecitabine	**(DC)**
Gemcitabine, Paclitaxel	**(GT)**
Gemcitabine, Carboplatin	**(GC)**

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 **paclitaxel (Taxol), docetaxel (Taxotere),** and **nab-paclitaxel; protein-bound paclitaxel (Abraxane),** 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 taxane-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[79, PMID:25759021]:** ***http://medicalxpress.com/news/2015-03-mechanism-glutamine-uptake-breast-cancer.html***

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

Docetaxel (Taxotere) vs. paclitaxel (Taxol): Docetaxel (Taxotere) produced a 32% anti-cancer response compared with **paclitaxel (Taxol)'s** 25% response, and patients taking **docetaxel (Taxotere)** had a 5.7 month progression-free survival (PFS) as opposed to those on **paclitaxel (Taxol)** who had a 3.6-month PFS. Patients taking **docetaxel (Taxotere)** had a 15.4-month overall survival (OS) as opposed to those on **paclitaxel (Taxol)** who experienced a 12.7-month OS. However, there is a small risk of permanent hair loss resulting from the use of **docetaxel (Taxotere)**.

Nab-paclitaxel; Protein-Bound Paclitaxel (Abraxane) vs. Paclitaxel (Taxol): Nab-paclitaxel (Abraxane) produced a 33% anti-cancer response compared with **paclitaxel (Taxol)'s** 19% response *(the 19% response rate to **paclitaxel (Taxol)** differed in this study from the 25% response rate in the above study)*. Patients taking **nab-paclitaxel (Abraxane)** had a 5.8-month PFS as opposed to those on **paclitaxel (Taxol)** who had a 4.2-month PFS, and patients taking **nab-paclitaxel (Abraxane)** had a 16.3-month OS as opposed to those on **paclitaxel (Taxol)** who experienced a 13.9-month OS. Only 9% of patients on **nab-paclitaxel (Abraxane)** experienced neutropenia (an abnormally low count of neutrophils, which are a type of white blood cell that helps fight off

infections), whereas 22% of patients taking **paclitaxel (Taxol)** had neutropenia. Whereas **paclitaxel (Taxol)** is administered with a toxic chemical solvent (liquid solution) in addition to the drug, **nab-paclitaxel (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 **nab-paclitaxel (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:**
http://kahlertregionalcancer.org/tools-resources/types-of-cancer/breast-cancer/stage-iv-breast-cancer/

Nab-Paclitaxel; Protein-Bound Paclitaxel (Abraxane) vs. Docetaxel (Taxotere): A randomized study of 302 previously untreated MBC patients who received either **nab-paclitaxel (Abraxane)** or **docetaxel (Taxotere)** demonstrated significantly longer progression-free survival (PFS) with **nab-paclitaxel (Abraxane)** than **docetaxel (Taxotere)** by both independent radiologist assessment (12.9 vs 7.5 months, respectively) and investigator assessment (14.6 vs 7.8 months, respectively). Furthermore, side effects such as neutropenia and fatigue were reduced in the group taking **nab-paclitaxel (Abraxane)**. **From:** ***https://ascopubs.org/doi/10.1200/JCO.2008.18.5397***

Caution Regarding Taxanes: Central nervous system 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 **paclitaxel (Taxol), Docetaxel (Taxotere),** and **nab-paclitaxel; protein-bound paclitaxel (Abraxane).** 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[38, PMID:16846533]:** ***https://breast-cancer-research.biomedcentral.com/articles/10.1186/bcr1516***

Capecitabine (Xeloda): Capecitabine (Xeloda) is a commonly used oral chemotherapy drug that is often used before other chemotherapy drugs are prescribed for MBC. **Capecitabine (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).

Capecitabine (Xeloda)/5-FU and DPD Deficiency: Before taking **capecitabine (Xeloda)** or 5-FU/fluorouracil (from which **capecitabine (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 **capecitabine (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. The FDA recently approved new labeling regarding 5-FU for injection and DPD deficiency**. From:** ***http://www.cancerresearchuk.org/about-cancer/cancers-in-general/cancer-questions/dpd-deficiency-and-fluorouracil*** and ***https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-safety-labeling-changes-regarding-dpd-deficiency-fluorouracil-injection-products***

Capecitabine (Xeloda)/5-FU Dose Reduction: Due to considerable side effects from **capecitabine (Xeloda)**, studies have been done on decreasing the drug's recommended dose and frequency. The current standard dose of **capecitabine (Xeloda)** as monotherapy is 1250 mg/m^2 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, two studies have shown that dose reductions can provide some relief. The X-7/7 study was a randomized clinical trial comparing the standard dose (above) with a fixed dose of 1500 mg of **capecitabine (Xeloda)** twice a day for 1 week on and 1 week off. This dosing schedule significantly reduced side effects, including hand foot syndrome, diarrhea, and mucositis, and showed no difference in effectiveness. However, there has been some controversy as to the study design in terms of effectiveness, as the study was not designed to show

non-inferiority. ***https://ascopubs.org/doi/abs/10.1200/JCO.2023.41.16_suppl.1007*** . Also, a dose of 1,000 mg/m^2 administered orally twice daily (morning and evening; equivalent to 2,000 mg/m^2 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 **capecitabine (Xeloda)** can be reduced, either when used alone or in combination with **docetaxel (Taxotere)**, to minimize adverse events without compromising efficacy in terms of time to progression or overall survival. **From [46, PMID:21856245]**

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, and 14 patients achieved stable disease. The most common side effects were anemia (43.8%), neutropenia (38.5%), nausea/vomiting (75.0%), and hair loss (62.5%). **From[78, PMID:22490573]: *http://www.ncbi.nlm.nih.gov/pubmed/22490573***

Caution Regarding Anthracyclines: **Doxorubicin (Adriamycin), 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 AI-only patients had a similar risk of stroke and cardiac ischemia (myocardial infarction and angina) as **tamoxifen (Nolvadex)-**only users, patients on AIs 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 [80, 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.

The National Comprehensive Cancer Network (NCCN) provides guidelines for treatment of people with MBC. The patient version can

be found here: ***https://www.nccn.org/patients/guidelines/content/PDF/stage_iv_breast-patient.pdf***. More information is available in the professional guidelines:
(***https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf***).
You can create a free account to view the professional guidelines. The information provided below is current as of 2023. Please see the above guidelines for the most recent updates.
In addition, the American Society of Clinical Oncology (ASCO) also provides guidelines.

HORMONAL THERAPY DRUGS BY MENOPAUSAL STATUS FOR HORMONE RECEPTOR-POSITIVE MBC PATIENTS BASED UPON NCCN GUIDELINES

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 is recommended for premenopausal patients and for men who take hormonal therapy. **Goserelin (Zoladex)** **Leuprolide (Lupron)** **Triptorelin (Trelstar)** **Selective Estrogen-Receptor Modulators (SERMs) with or without an LHRH:** SERMs attach themselves to the hormone receptor in the cancer cell, thus blocking estrogen from linking to the cell's hormone receptor. SERMs may be given alone or paired with the cancer drug **everolimus (Afinitor)**. **Tamoxifen (Nolvadex)** **Toremifene (Fareston)** **Aromatase Inhibitors (AIs),** which lower estrogen levels by keeping one enzyme (called aromatase) from changing other hormones into estrogen. In some instances, AIs may be paired with other cancer-directed drugs such as **palbociclib (Ibrance), ribociclib (Kisqali), abemaciclib (Verzenio),** and **everolimus (Afinitor).** **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 other cancer-directed drugs such as **palbociclib (Ibrance), ribociclib (Kisqali), abemaciclib (Verzenio), and everolimus (Afinitor) (or anastrozole (Arimidex)** in specific circumstances). **Fulvestrant (Faslodex)**
Postmenopausal	**Aromatase Inhibitors (AIs),** which lower estrogen levels by keeping one enzyme (called aromatase) from changing other hormones into estrogen. In some instances, AIs may be paired with **palbociclib (Ibrance), ribociclib (Kisqali), abemaciclib (Verzenio), and everolimus (Afinitor).** **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 (Faslodex)** may be given alone or paired with **palbociclib (Ibrance), ribociclib (Kisqali), abemaciclib (Verzenio),** and **everolimus (Afinitor) (or anastrozole (Arimidex) or alpelisib (Piqray)** in specific circumstances). **Fulvestrant (Faslodex)** **Selective Estrogen-Receptor Modulators (SERMs) with or without an LHRH:** SERMs attach themselves to the hormone receptor in the cancer cell, thus blocking estrogen from linking to the cell's hormone receptor. SERMs may be given alone or paired with the cancer drug **everolimus (Afinitor)**. **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)** **<u>Other Hormonal Therapies:</u>** **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 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 **[81, 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 30-mg daily dose of estrogen to a low 6-mg daily dose, and 30% of patients in 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[82, PMID:PMC3460383]**

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[27, PMID:PMC3656649]:** ***http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3656649***

Toremifene (Fareston):

Some people do not respond to **tamoxifen (Nolvadex)** due to a flaw in their CYP2D6 genetic pathway (as described under ***Tamoxifen (Nolvadex)*** below). Patients who do not respond to **tamoxifen (Nolvadex)** 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 **toremifene (Fareston)**, which is a selective estrogen receptor modulator (SERM) like **tamoxifen (Nolvadex),** may be a viable choice for postmenopausal (not premenopausal) patients. **From:** ***https://ascopubs.org/doi/abs/10.1200/jco.2011.29.15_suppl.e13068***

Fulvestrant (Faslodex):

Fulvestrant (Faslodex) is a widely used hormonal therapy drug for hormonally sensitive postmenopausal patients after an aromatase inhibitor (AI) has failed. **Fulvestrant (Faslodex)** is classified as a selective estrogen receptor downregulator (SERD), which works by blocking or breaking down the estrogen receptors on cells.

Fulvestrant (Faslodex) was approved in 2017 as a first-line therapy for MBC patients in the US and Europe. One study indicated that **fulvestrant (Faslodex)** improved overall survival (OS) by 5.7 months compared with **anastrozole (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 **fulvestrant (Faslodex)** reduced the risk of death by 30% compared with **anastrozole (Arimidex)**. The median OS was 54.1 months with **fulvestrant (Faslodex)** compared with 48.4 months with **anastrozole (Arimidex)**. Furthermore, using **fulvestrant (Faslodex)** as a first-line therapy for this population also improved time to progression, which was 23.4 months for **fulvestrant (Faslodex)** and 13.1 months for **anastrozole (Arimidex)**. **From[83, PMID:14535531; 84; 85, PMID:24317176]:**

http://www.researchgate.net/publication/9057460_Sequential_hormonal_therapy_for_metastatic_breast_cancer_after_adjuvant_Tamoxifen_or_anastrozole and ***http://www.lbbc.org/news-opinion/study-finds-higher-dose-fulvestrant-reduces-risk-death***

Fulvestrant (Faslodex) in combination with **ribociclib (Kisqali)** 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 **ribociclib (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 PFS at the time of data cut-off was 20.5 months in patients randomized to receive **ribociclib (Kisqali)** and **fulvestrant (Faslodex)**, compared with 12.8 months in those randomized to receive **fulvestrant (Faslodex)** alone. **From:**

http://www.targetedonc.com/conference/asco-2018/both-frontline secondline-benefit-with-ribociclibfulvestrant-in-hrher2-breast-cancer-across-frontline-and-secondline

Fulvestrant (Faslodex), which is injected in the butt, can be a bit painful. For intramuscular injections such as those for **fulvestrant (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.

Megestrol Acetate (Megace):

Most breast cancer patients are unaware of an older hormonal therapy drug called **megestrol acetate (Megace)**. **Megestrol acetate (Megace)** acts in a similar way to the hormone progesterone, which can be an effective treatment for advanced breast cancer. **Megestrol acetate (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 (Nolvadex) 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 (Nolvadex)**, 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 (Nolvadex)** 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 (Nolvadex)**, breast cancer patients with genetic alterations of CYP2D6 who are considered to be poor metabolizers of **tamoxifen (Nolvadex)** 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 **anastrozole (Arimidex)** following 2 years of **tamoxifen (Nolvadex)** therapy. In fact, for the women who switched to **anastrozole (Arimidex)**, there was a tendency towards a reduction in the odds of reduction for a recurrence. **From[86, 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 (Nolvadex)** effectiveness, prompting recommendations against testing. But in a Mayo Clinic study, researchers found that previous studies that 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[87, 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 (Nolvadex)**. **From[4, PMID:27022119]**
In a study of rats with human breast tumors, exposure to dim light at night made their tumors resistant to **tamoxifen (Nolvadex)**, according to data published in *Cancer Research*. The negative effects of dim light exposure on **tamoxifen (Nolvadex)** 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 (Nolvadex)** 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 (Nolvadex)** 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[88, 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 (Nolvadex)**. 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***

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[31, PMID:24799487]**

In breast cancer, mutation of the *TP53* gene is the most commonly identified genetic defect, followed by the *PIK3CA* mutation. **From[89, PMID:24074787; 90; 91]:** ***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 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 **everolimus (Afinitor)** can be used together with **exemestane (Aromasin)** for postmenopausal hormone receptor + HER2- women whose MBC has become resistant

to hormone therapy. **Everolimus (Afinitor)** belongs to the class of drugs known as mammalian target of rapamycin (mTOR) inhibitors mentioned above. Data suggest that mTOR inhibitors currently in use, such as **everolimus (Afinitor)**, will be ineffective against cancers that have a mutation in either the *KRAS* or *BRAF* gene. **From[92, 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.
Analysis of several studies showed that using a beta blocker called **carvedilol (Coreg)**. (Beta blockers slow down the heart and lower blood pressure) can reduce cardiotoxicity and a type of heart damage called ventricular remodeling but not another type of heart problem called LVEF decrease. Another study showed that Coenzyme Q10 (CoQ10) may also afford some heart protection for women undergoing chemotherapy and trastuzumab (Herceptin), which can compromise heart function. **From:**
https://pmc.ncbi.nlm.nih.gov/articles/PMC6476829/ and
https://pmc.ncbi.nlm.nih.gov/articles/PMC10652675/
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), palbociclib (Ibrance), ribociclib (Kisqali), and abemaciclib (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*.

The National Comprehensive Cancer Network (NCCN) provides guidelines for treatment of people with MBC. The patient version can be found here: ***https://www.nccn.org/patients/guidelines/content/PDF/stage_iv_breast-patient.pdf***. More information is available in the professional guidelines: (***https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf***).

You can create a free account to view the professional guidelines. The information provided below is current as of 2023. Please see the above guidelines for the most recent updates.

In addition, the American Society of Clinical Oncology (ASCO) also provides guidelines.

TARGETED THERAPY DRUGS FOR MBC PATIENTS
BASED UPON NCCN GUIDELINES

Targeted therapy agent	Type of MBC	Approved/recommended treatment	Notes
Trastuzumab (Herceptin) * **Ogivri, Herzuma, SB3, Trazimera, and Kanjinti** are FDA-approved biosimilar drugs to Herceptin. **Trazimera** was also approved by the EU in 8/18.		**Trastuzumab (Herceptin) and biosimilars** are approved in combination with **pertuzumab (Perjeta)** and a Taxane for first-line treatment. In later lines, it can be combined with other chemotherapy or **lapatinib (Tykerb).** For HR+, HER2+ patients, it may be combined with hormonal therapy, with or without **lapatinib (Tykerb).** or **pertuzumab (Perjeta)**	**Trastuzumab (Herceptin)** was approved by the FDA for use in 1998
trastuzumab and hyaluronidase-oysk (Herceptin Hylecta)	HER2+	**trastuzumab and hyaluronidase-oysk (Herceptin Hylecta)** is a subcutaneously injected version of **trastuzumab (Herceptin)** and hyaluronidase-oysk that was approved combination with **pertuzumab (Perjeta)** and a taxane as first-line treatment for	FDA-approved in 2019

		patients with HER2+ MBC, and as a stand-alone therapy for HER2+ MBC patients who have received at least one prior chemotherapy regimen	
Lapatinib (Tykerb)	HER2+	In combination with **trastuzumab (Herceptin)** or biosimilar, or with chemotherapy. For HR+, HER2+ patients, it may be combined with an aromatase inhibitor, with or without **trastuzumab (Herceptin)** or a biosimilar.	Approved for use in 2007
Pertuzumab (Perjeta)	HER2+	In combination with **trastuzumab (Herceptin)** - or a biosimilar - and a taxane as first-line treatment. It has been approved with **trastuzumab (Herceptin)** or a biosimilar as a later-line therapy. For HR+, HER2+ patients, it is approved with **trastuzumab (Herceptin)** (or a biosimilar) and hormonal therapy.	Approved for use in 2012

Ado-Trastuzumab Emtansine (TDM-1; Kadcyla)	HER2+	As a single agent after failure of **trastuzumab (Herceptin), pertuzumab (Perjeta)** and a taxane	Approved for use in 2013
Pembro-lizumab (Keytruda)	Metastatic	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. Also approved for TMB-H (tumor mutational burden high) tumors. Approved for PD-L1-positive TNBC MBC patients in combination with chemotherapy.	Approved for this subset of patients in 2017 and for TMB-H patients in 2020 Approved in 2020 for TNBC MBC patients whose tumors are PD-L1 positive
Everolimus (Afinitor)	Hormone receptor-positive, HER2-MBC	In combination with **letrozole (Femara), anastrozole (Arimidex), exemestane (Aromasin), fulvestrant (Faslodex), tamoxifen (Nolvadex), or**	Approved for use in 2012

		toremifene (Fareston)	
Palbociclib (Ibrance)	Hormone receptor-positive, HER2-MBC	In combination with **letrozole (Femara), anastrozole (Arimidex), exemestane (Aromasin), fulvestrant (Faslodex)**	Approved in 2/2015 and expanded in 4/2017
Ribociclib (Kisqali)	Hormone receptor-positive, HER2-MBC	In combination with **letrozole (Femara), anastrozole (Arimidex), exemestane (Aromasin), fulvestrant (Faslodex)**	Approved for use in post-menopausal patients in 3/2017, and for pre-menopausal patients in 7/2018
Abemaciclib (Verzenio)	Hormone receptor-positive, HER2-MBC	In combination with **letrozole (Femara), anastrozole (Arimidex), exemestane (Aromasin), fulvestrant (Faslodex)**, 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	Approved in the US in 10/2018 and approved in Europe in 6/2019

		BRCA-mutated disease who are eligible for **talazoparib (Talzenna).** Patients must be selected for **talazoparib (Talzenna)** based on an FDA-approved companion diagnostic.	
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	FDA-approved 1/2018 and approved in Europe 4/2019
Alpelisib (Piqray)	Hormone receptor-positive, HER2-men and post-menopausal women with a *PIK3CA* mutation	In combination with **fulvestrant (Faslodex)** in patients for whom an endocrine therapy failed	FDA-approved in May 2019
Larotrectinib (Vitrakvi)	Metastatic	Metastatic cancer of any type that has a *NTRK* gene fusion without a known acquired resistance mutation	FDA approved in Nov. 2018
Entrectinib (Rozlytrek)	Metastatic	Metastatic cancer of any type that has a *NTRK* gene fusion without a known acquired resistance mutation	FDA approved in Aug. 2019

Atezolizumab (Tecentriq)	TNBC MBC that expresses PD-L1	In combination with **paclitaxel (Abraxane)** as initial treatment for TNBC MBC patients whose tumors express PD-L1	FDA-approved in March 2019 and approved in Europe in Aug. 2019. Taken off the US market in Aug. 2021. Still available in Europe.
fam-trastuzumab deruxtecan-nxki (T-DXd; Enhertu)	HER2+	Approved for HER2+ MBC that progressed after at least 1 prior line of HER2-directed therapy, and for HER2-low MBC for patients who have received a prior chemotherapy.	FDA-approved for HER2+ in Dec. 2019 and FDA-approved for HER2-low in Aug. 2022
Neratinib (Nerlynx)	HER2+	In combination with **capecitabine (Xeloda)** for HER2+ MBC that progressed after at least 2 prior lines of HER2-directed therapy	FDA-approved in Feb. 2020
Tucatinib (Tukysa)	HER2+	In combination with **capecitabine (Xeloda)** and **trastuzumab (Herceptin)** or a biosimilar for HER2+ MBC that progressed after at least 1 prior line of HER2-directed therapy	FDA-approved in April 2020

Sacituzumab govitecan-hziy (Trodelvy)	TNBC MBC	After two or more prior lines of therapy for metastatic disease.	FDA-approved in April 2020
Phesgo	HER2+ MBC	An injectable (not infused) combination of **pertuzumab, trastuzumab, and hyaluronidase–zzxf**	FDA-approved in June 2020
Margetuximab (Margenza)	HER2+ MBC	In combination with chemotherapy for HER2+ MBC patients who have received two or more prior anti-HER2 regimens, at least one of which was for MBC.	FDA-approved in Dec. 2020
Dostarlimab-gxly (Jemperli)	Metastatic	Mismatch repair deficient (dMMR) solid tumors that have progressed following prior treatment and for which there is no viable standard therapy	FDA-approved in Aug. 2021

Trastuzumab (Herceptin), lapatinib (Tykerb), pertuzumab (Perjeta), and trastuzumab emtansine (T-DM1; 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.

Lapatinib (Tykerb) and trastuzumab emtansine (T-DM1; 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.

CDK4/6 Inhibitors: In Sept. 2019, the FDA issued a warning that the CDK4/6 inhibitors **palbociclib (Ibrance), ribociclib (Kisqali), and abemaciclib (Verzenio)** may cause rare but severe inflammation of the lungs. Although the overall benefit of CDK4/6 inhibitors is still considered greater than the risks when used as prescribed, patients taking a CDK4/6 inhibitor are advised to notify their medical teams if there is a new or worsening symptom involving the lungs, as this may indicate a rare but life-threatening condition that can lead to death. Symptoms to watch for include difficulty or discomfort with breathing and/or shortness of breath while at rest or with low activity. **From:** ***https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-rare-severe-lung-inflammation-ibrance-kisqali-and-verzenio-breast-cancer***

Ribociclib (Kisqali): Unlike **palbociclib (Ibrance) or abemaciclib (Verzenio), ribociclib (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).

Everolimus (Afinitor):

Everolimus (Afinitor) may be used in conjunction with either an aromatase inhibitor, **fulvestrant (Faslodex), or tamoxifen (Nolvadex)** for postmenopausal hormone receptor-positive patients after they develop resistance to hormonal therapies.

Patients taking **everolimus (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, **everolimus (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. **Everolimus (Afinitor)** may also increase blood sugar and/or lipid levels, so they should be regularly monitored as well. Therefore, patients taking **everolimus (Afinitor)** should be monitored closely during treatment for these conditions.

In a trial for advanced breast cancer, 63% of those taking **everolimus (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 **everolimus (Afinitor)** users, including more than 2,700 deaths and more than 3,100 hospitalizations. Notably, as per a database-based study of 3,556 **everolimus (Afinitor)** users, 46% were hospitalized or visited the Emergency Room during their treatment. **From:** ***https://www.breastcancer.org/treatment/targeted-therapy/afinitor***

A less severe but very common side effect of **everolimus (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 **everolimus (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 10-mg dose of **everolimus (Afinitor)** are encouraged to speak with their doctor about going on a reduced dose of 5 mg.

Several people on various MBC online forums have reported developing metastasis to the liver or lung after taking **everolimus (Afinitor)**, but as of January 2020, no studies were located which corroborated this phenomenon. Therefore, the possibility that **everolimus (Afinitor)** may in some way precipitate liver and/or lung metastasis remains anecdotal, yet it is something to be aware of.

22. 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 membrane 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[93, 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:**
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.

23. 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 be 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 1/2 clinical trial** is a study that tests the safety, side effects, and best dose of a new treatment. Phase 1/2 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 1 and 2 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**: ***https://www.cancer.org/cancer/managing-cancer/making-treatment-decisions/clinical-trials/what-you-need-to-know/phases-of-clinical-trials.html***

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 trial. 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 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 Institutes 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 metastatic 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.

Metastatic Trial Search (***https://www.breastcancertrials.org/bct_nation/mts/mtsResult.seam?brca=na&ar=na&pr=na&pi3k=na&partnerSite=mtt&er=na&her2=na&pdl1=na***) is a free trial matching application designed by and for patients that matches a patient to clinical trials specifically for MBC based on the profile provided by the patient. Trial summaries are written in patient-friendly language. Users can browse trials and/or filter trials by location, phase, trial type, or mutation. Free appointments with a Clinical Trial Navigator are available. Users can also sign up for a weekly email that lists trials that match their profile.

For readers in Canada, this is a link for Canada-based clinical trials: ***https://health-products.canada.ca/ctdb-bdec/index-eng.jsp***

For readers in the UK, this is a link for UK-based clinical trials: ***https://bepartofresearch.nihr.ac.uk/results/search-results?query=&location=***

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

For readers in Australia and New Zealand, this is a link for Australian-based and New Zealand-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*** And in March 2019, Airbnb announced a

strategic partnership with the Cancer Support Community. Through this collaboration, the Airbnb community will provide free housing for cancer patients traveling for treatment and their caregivers, provided they meet certain geographic and income criteria. **From:** ***https://annualreport.cancersupportcommunity.org/airbnb-medical-stays-program***

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***

Items to Understand When Deciding Whether to Participate in a Clinical Trial

The Phase of the trial

If this is a Phase 2 or Phase 3 trial, what was the effectiveness of the experimental therapy in the prior study, and what type and degree of toxicities were experienced by patients?

What are the inclusion and exclusion criteria for the trial?

Whether there is a possibility of receiving a placebo (sugar pill) instead of the experimental drug. If a group of patients may receive a placebo, what drug(s) will they receive to treat their disease?

Whether there is a required washout ("run-in") period prior to entering the trial whereby the patient must stay off all medication that would normally treat their disease.

If a washout period is required, how long is it? Often it lasts for 28 days, which may pose a risk in terms of disease progression and mortality.

How will the therapy be administered (pill, IV, other?)

What risks and side effects may be experienced on the experimental drug?

How often will the patient need to visit the hospital or clinic? Are there any tests, procedures, or administration of study medication that can be done in the patient's hometown? Can any of the visits be done remotely (i.e., via Telemed)?

Will the patient need to stay in the hospital? If yes, how often and for how long, and who will cover inpatient hospital costs?

What costs may the patient incur on - and traveling to - the trial, and which of these costs will be covered (and by whom)?

What is the nature and frequency of tests given to patients on the trial?

Who will cover the costs of these tests?

If the patient becomes ill due to the experimental drug, will the patient's related expenses be reimbursed? If yes, by whom?
Who will oversee the patient's medical care while they are on the trial?
Who may the patient speak with about questions they may have during and after the trial, and how can they be contacted?
Who can help answer any specific questions from the patient's insurance company?
How and when will it be determined whether the treatment is working?
Is the timing of the trial appropriate for the patient's situation? (For example, a newly diagnosed patient may prefer to receive standard of care treatment instead of immediately entering a clinical trial, especially if the standard of care is generally considered effective for their subtype of MBC).
Why is this particular clinical trial being recommended? This is a critical question, and if a satisfactory answer is not provided, the patient may want to reconsider whether they wish to enter the trial.
Similar to the above, how do the possible risks and benefits of this trial compare to those of the standard treatment?
What are the credentials and research experience of the physician and study staff?
How long is the trial expected to last?
If the patient decides to drop out of the trial, they may do so at any time without repercussion.
If one group of patients in the trial fares considerably better than another group, can the patient switch to the group with the better outcome? If yes, at what point would this be possible?
Will the patient be informed about what treatment they are receiving on the trial? Is yes, at what point will it be disclosed?
If the patient has a good response to the experimental therapy, may they continue to take it after the trial has stopped?
Will the patient receive notification of the outcome of the trial? If yes, when is it expected to be provided?

24. 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.

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In 2019, the FDA launched "Project Facilitate," a call center pilot program to assist oncology healthcare providers in requesting access to investigational therapies for patients with cancer. Project Facilitate is a single point of contact whereby FDA oncology staff will help physicians and their healthcare team through the process to submit an Expanded Access request for an individual cancer patient. Healthcare providers may call Project Facilitate at 1.240.402.0004 or email OncProjectFacilitate@fda.hhs.gov Patients and families with questions can call FDA's Division of Drug Information at 1.301.796.3400 or email druginfo@fda.hhs.gov

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: If 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 the 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 as 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***

25. 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[94, PMID:21343379]: *http://www.ncbi.nlm.nih.gov/pubmed/21343379***

Furthermore, when previously diagnosed metastatic breast cancer occurs in a new organ, and/or when several MBC treatments have failed, it is recommended that a new biopsy be undertaken if possible because the pathology (hormone receptor status and/or HER2 status) might have changed. If this is the case, a new type of treatment might be warranted. It is widely recognized that MBC changes over the course of the disease, as evidenced by a study whereby multiple biopsies from various organs were taken from 82 MBC patients during tumor progression, and the re-conversion (change) rates for ER and PR were surprisingly high at 26.83% and 35.36%, respectively. **From: *https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5342130/***

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.

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 staff members 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 receptors degrade 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 factor 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[95, 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***

26. 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 diagnosis and treatment of primary benign and malignant tumors of the bones and perform surgery.

According to Dr. Catherine H. Van Poznak, Medical Oncologist at the University of Michigan, after a new treatment is initiated, a small fraction of patients whose bone metastasis is actually responding well to the therapy may experience a temporary "flare" of their symptoms, including increased bone pain, a rise in tumor markers, and/or an apparent temporary worsening of disease in imaging tests. Therefore, treatment should not be changed unless there has been a period of due diligence over time. (Note: A lack of flare does not necessarily mean the treatment is not working!).

Lastly but importantly, although external beam radiation therapy has generally been the standard-of-care for painful bone lesions, in the past it has not been used for asymptomatic lesions except for oligometastases. But according to the results of a Phase 2 randomized study of 78 adults with a metastatic solid tumor malignancy and more than five metastatic bone lesions (including at least one asymptomatic high-risk bone lesion), it was determined that treating the asymptomatic lesions with radiation reduced the number skeletal-related events (SREs) and extended overall survival compared with patients who received no radiation for asymptomatic lesions. At the end of one year, SREs occurred in 1 of 62 lesions (1.6%) for patients in the radiation arm compared to 14 of 49 lesions (29%) for patients who received no radiation. After the first three months, patients in the radiation arm reported less pain than patients who didn't undergo radiation, and treating the lesions with even low doses of radiation seemed adequate to prevent the lesion from progressing and causing problems. **From:** ***https://medicalxpress.com/news/2022-10-therapy-high-risk-asymptomatic-bone-metastases.html***

TREATMENTS FOR BONE METASTASIS

Once bone metastasis has been diagnosed, systemic 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/denosumab (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 denosumab (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 **zoledronic acid (Zometa)** and **denosumab (Xgeva). Pamidronate (Aredia),** which is a bisphosphonate, can also be used. In some countries outside the US, the drugs **clodronate and ibandronate (Boniva)** have been approved for MBC patients with bone metastasis. **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, **denosumab (Xgeva)** delayed the time to bone complications compared to **zoledronic acid (Zometa),** although overall survival was similar. **From**: ***https://pubmed.ncbi.nlm.nih.gov/22392458/***

  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 denosumab (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 **denosumab (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 **denosumab (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 (Zometa)** every 12 weeks after one year of monthly administration was as effective as continuing to receive it monthly. **From:** ***http://www.sciencedaily.com/releases/2014/05/140530142414.htm***

Side effects from zoledronic acid (Zometa): Some patients report feeling unwell for several days after receiving a **zoledronic acid (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 **acetaminophen (Tylenol)** or **ibuprofen (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/denosumab (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 (ESMO) 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[52, PMID:PMC5834023]:** ***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:** ***https://www.breastcancer.org/types/metastatic/bone-metastasis*** and ***https://www.yalemedicine.org/news/metastatic-bone-cancer-aorif-procedure***
- **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:**

https://www.sciencedaily.com/releases/2013/06/130602144337.htm

- **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.

  - *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**: ***https://www.breastcancer.org/types/metastatic/bone-metastasis***

- **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 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:**
https://americanbonehealth.org/blog-post/how-do-phytates-impact-calcium-absorption/

27. 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.

28. 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 - although controversial - 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)**
- **Surgery**
- **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 membranes of the tumor. The cancer cells die, and the healthy tissue remains unharmed.

- *Radiofrequency Ablation (RFA):* Radiofrequency ablation, also known as RFA, is a technique of heating up liver cancers with probes inserted into the tumors.
- *Histotripsy*: Histotripsy uses ultrasound waves to break down tumors in the liver. This technique may cause fewer side effects than radiation because it better targets only the tumor. Histotripsy was FDA approved in the fall of 2023 for treating both primary liver cancers and metastases to the liver, such as from MBC. You can find histotripsy at the following locations: ***https://histosonics.com/find-edison-provider/*** and ***FDA Awards HistoSonics Clearance of its First-of-a-Kind Edison® Histotripsy System - HistoSonics*** and ***https://news.umich.edu/tumor-destroying-sound-waves-receive-fda-approval-for-liver-treatment-in-humans/*** ***https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9404673/***

- **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[96, 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 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[97, PMID:23173748]: *http://www.ncbi.nlm.nih.gov/pubmed/23173748***

- **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*: http://www.sciencedaily.com/releases/2014/03/140324133234.htm***

That said, the author has read several patient accounts, some commenting that the procedure was not successful for them and others for whom it was. Many patients disclosed that they were greatly fatigued afterwards. Hence, 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***

- **Surgery:** A retrospective study compared outcomes of two groups of MBC patients with 1 to 5 liver metastases. One group of 29 patients (Group 1) had undergone systemic therapy plus surgery, and the other group of 33 patients (Group 2) had systemic therapy only. There was no 90-day mortality after surgery. Median overall survival in Group 1 was 77 versus 28 months in Group 2. Factors in addition to surgery that may have influenced survival in Group 1 patients were a longer disease-free interval and more estrogen receptor-positive tumors than Group 2 patients**. From:** ***https://www.practiceupdate.com/content/surgical-treatment-of-breast-cancer-liver-metastases/97134***

- **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[99, 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. For example, one patient with ascites claimed that the prescription diuretic drugs Lasix and Spironolactone helped her.

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 it 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 may be 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 and 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:

Bevacizumab (Avastin): In one study, nine patients with refractory malignant ascites were given **bevacizumab (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 (Avastin)** at 5 mg/kg monthly. Malignant ascites resolved without re-accumulating or repeat paracentesis in all nine patients after a single intraperitoneal dose of **bevacizumab (Avastin)** over a median observation period of over two months. **From[100]:** ***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. **Catumaxomab (Removab)** was evaluated as part of a Phase 1/2 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 (Removab)** 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 (Removab)** 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[99, 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 (Removab)** 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 (Removab)** can be administered in relatively frail outpatients, achieving good ascites control. A survival benefit was seen in fit patients who received complete IP **catumaxomab (Removab)** treatment and were able to undergo subsequent systemic therapy. **From[101]:** ***http://www.medpagetoday.com/MeetingCoverage/SGO/44939***

Mistletoe extract (Iscador): 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[102, 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 (Sandostatin LAR®)** 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 (Sandostatin LAR®)-**treated patients described less abdominal bloating, abdominal discomfort, and shortness of breath at 1 month. As prescribed in this trial, **octreotide (Sandostatin LAR®)** did not seem effective in prolonging the time to next paracentesis, although symptoms had improved. **From[103, 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 (Sandostatin LAR®)** (described above) in cases of malignant bowel obstruction, as well as in instances of trapped “loops” of bowel that are non-operable. **Octreotide (Sandostatin LAR®)** 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[104, PMID:22859627]: *http://www.cfp.ca/content/58/6/648.full***

29. 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 non-small cell lung carcinoma (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, 2 years later:

88% of patients achieved a complete disappearance of cancer at the site of RFA, which lasted for at least 1 year.

Overall survival at 1 year was 92% for patients with metastasis from sites other than the colon

Overall survival at 2 years was 64% for metastasis from sites other than the colon

From: *https://pubmed.ncbi.nlm.nih.gov/18565793/*

- **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[105, PMID:23391172]:**

- **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 determine 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 is 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 receptor positivity, 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 it 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 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, CDK4/6 inhibitors, and radiation, MBC patients may be particularly susceptible.

30. 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. Consider requesting an MRI at any signs of possible brain metastasis or any time there is disease progression.

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.

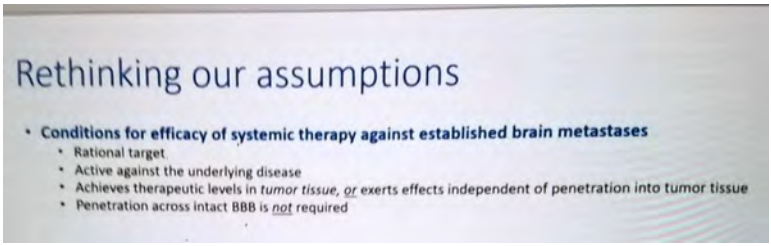
- **HER2+**
- **TNBC**
- **Triple-Positive MBC**
- **Patients with CK-19 mRNA-positive Circulating Tumor Cells** (CTCs)

From:
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[107, PMID:25144276]:** ***http://www.cancernetwork.com/oncology-journal/updates-management-breast-cancer-brain-metastases***

That said, at the FDA's March 22, 2019 forum entitled, *"Product Development for Central Nervous System (CNS) Metastases,"* it was

disclosed (as per the fourth bullet below) that penetration across the intact BBB is not required for a drug to exhibit a degree of efficacy in treating brain metastases. This represents a considerable paradigm shift, and several drugs that do not freely penetrate an intact BBB yet display antitumor efficacy were used as examples (including **lapatinib (Tykerb), pembrolizumab (Keytruda), capecitabine (Xeloda), trastuzumab emtansine (T-DM1; Kadcyla),** and others).



The FDA forum also indicated that studies dating back to 2010 have demonstrated that CNS metastases may be molecularly different than disease at other sites. This challenges the assumption that a biopsy from a primary tissue or other metastatic sites can be used to make treatment decisions about CNS metastases or identify optimum targets. More recent studies have confirmed the ability of antibody-based treatments and small molecule drugs to enter the brain and be effective for treating brain metastases. From: ***https://www.medpagetoday.com/meetingcoverage/mbcc/97535***

Patients with brain metastases are encouraged to visit this comprehensive website called MBC Brain Mets that contains information about treatments, finding clinical trials, and more: ***https://mbcbrainmets.org/***

The following section contains detailed information about treatments such as radiotherapy, surgery, and drugs that are used for patients with brain metastases.

In an excellent 2019 video about the use of radiotherapy for brain metastasis, Dr. Paul Brown, Professor of Radiation Oncology at the Mayo Clinic, suggested the following guidelines for radiation treatment irrespective of where the cancer originated (breast, lung, colon, etc.).

Those wishing to view the video may visit: ***https://vimeo.com/321234317/33959e4ee9*** Another source for the information below is Adam Brufsky, MD, PhD, Professor of Medicine at the University of Pittsburgh School of Medicine ***https://www.medscape.com/viewarticle/917894***

- **For patients with a single large brain metastasis,** surgery plus stereotactic radiosurgery (SRS) is considered the standard of care. (Adding whole-brain radiotherapy (WBRT) can help prevent additional brain metastases, but it fails to improve overall survival (OS) and can significantly diminish cognitive capabilities and quality of life (QOL)).

- **For patients with one or two metastases** that are relatively close together but in an area of the brain where the surgeon feels it won't cause too much damage to remove them, they may be excised surgically. If the metastases are in an area of the brain where the surgeon feels it would cause too much damage to remove them, SRS with CyberKnife, which is single focused-dose radiation, is a viable option.

- **For patients with oligometastases (defined in the video as one to four brain metastases),** SRS is recommended. Adding WBRT thereafter helps to prevent additional brain metastases, but does not improve OS and can significantly degrade cognitive abilities and QOL. Therefore, SRS is considered the standard of care for these patients.

- **For patients with up to 10 metastases:** According to Dr. Brufsky, many clinicians use CyberKnife in a series - two or three times for up to 10 metastases - depending on their location in the brain.

- **For patients with multiple (widespread) brain metastases, or patients who have a rapid recurrence (i.e. within a few months) of brain metastases treated with SRS,** hippocampal avoidance (HA) WBRT with **memantine HCL (Namenda)** is recommended, although using SRS alone for patients with up

to 10 brain metastases may also be a viable option. (The role of systemic therapy in this context is still being explored).

HA WBRT is a special form of WBRT that spares the hippocampus (a small region of the brain that is primarily associated with memory and spatial navigation) from being targeted by radiation. HA WBRT is accomplished by using intensity-modulated radiation therapy (IMRT), which is an advanced mode of high-precision radiotherapy that uses computer-controlled linear accelerators to deliver precise radiation doses to a malignant tumor or specific areas within the tumor. **Memantine HCL (Namenda)** is an Alzheimer's drug that can help prevent cognitive decline.

Non-Drug treatments for brain metastasis

- **Brain Surgery**
- **Interstitial Laser Ablation (ILA, LA,** or **LITT)**
- **Proton Therapy**
- **Radiosurgery** such as:
  - *CyberKnife*
  - *Gamma Knife*
- **Whole Brain Radiation Therapy (WBRT)**

These procedures are described below:

- **Brain surgery** may be used for one or two large metastases that need to be removed immediately because of potential brain damage, or when the metastasis is too big for radiosurgery.

- **Interstitial Laser Ablation (ILA, LA,** or **LITT):** Interstitial laser ablation is an emerging technique to treat primary and metastatic brain tumors that can be hard to reach with conventional surgery. It is performed by drilling a very small hole about the size of a pencil's diameter, inserting a laser catheter into the tumor, and heating it to temperatures high enough to kill the tumor. The catheter is implanted using advanced computer imaging, and the laser is guided through the catheter with real-time MRI, enabling neurosurgeons to limit thermal energy delivery only to the tumor. Most patients can go home the day of or the day after treatment. Key indications for the procedure include inoperable brain tumors in the thalamus or insula, recurrent metastases after stereotactic

radiation, and radiation necrosis that has led to swelling. In a retrospective study of 133 intracranial lesions in 120 patients who were treated with ILA, including gliomas and cancer metastasis, median progression-free survival (PFS) was not yet reached for the metastasis cohort, and overall survival (OS) was 17.2 months. The study concluded that ILA is a safe and efficacious treatment for a variety of intracranial pathologies, can be tailored to treat difficult-to-access lesions, and may offer an alternative to open craniotomy in properly selected patients. **From:** ***https://www.karger.com/Article/FullText/485387***

- **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***

- **Stereotactic Radiosurgery (SRS):** The term "radiosurgery" is misleading because the procedure does not involve surgery. Radiation is given from the outside of the head without having to cut into the skull. This is a procedure that aims for 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.

In the past, radiosurgery was generally not used for more than three metastases at a time, or for metastases that are larger than approximately 3 centimeters. However, more and more patients and their doctors are going outside these guidelines, treating more than three metastases as well as metastases 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[108, 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.

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.

- *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. WBRT 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:** ***http://www.brainmetsbc.org/en/content/current-treatments-brain-metastases***

  As previously mentioned, there is a type of WBRT that is a "**hippocampus sparing procedure,**" which may help to preserve a degree of memory that might otherwise be lost because of the procedure. It can (and should) be combined with **memantine HCL (Namenda)**, which is an Alzheimer's drug that can help prevent cognitive decline. 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 WBRT without the hippocampus sparing procedure**. From[109, PMID:25349290]**: ***https://vimeo.com/321234317/33959e4ee9***

A retrospective study reviewed the status of 253 breast cancer patients with brain metastasis who were treated with WBRT. The results were consistent with mounting evidence that histone deacetylase **(HDAC) inhibitors such as valproic acid (VPA; Valproic) synergize with radiation to improve patient outcomes**. **Valproic acid (VPA; Valproic)** 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 **valproic acid (VPA; Valproic)** with WBRT had a 6-month longer overall survival than those who did not receive **valproic acid (VPA; Valproic)**. **From[110, PMID:26482599]:** ***http://www.sciencedirect.com/science/article/pii/S0167814015005514***

Trastuzumab (Herceptin) can also be combined with WBRT for HER2+ patients, as per the results of a study of 31 patients presenting with HER2+ metastatic breast cancer in the brain and treated with HBRT and **trastuzumab (Herceptin)**. After WBRT was completed, radiologic responses were observed in 23 patients (74.2%), including 6 patients (19.4%) who had a complete radiologic response and 17 patients (54.8%) with a partial radiologic response. **From[111, 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:

- **Abemaciclib (Verzenio)**
- **Ang1005** – *(Not Yet FDA-Approved for MBC Patients)*
- **Aprepitant (Emend)**

- **Bevacizumab (Avastin) and Irinotecan (CPT-11; Camptosar)** *(Not Yet FDA-Approved for MBC Patients)*
- **Boswellia Serrata**
- **Chemotherapy Drugs**
- **Dexamethasone (Decadron)**
- **Entrectinib (Rozlytrek) for NTRK fusion-positive solid tumors**
- **Fam-trastuzumab deruxtecan-nxki (T-DXd; Enhertu)**
- **Hormonal Therapies**
- **Lapatinib (Tykerb) and Capecitabine (Xeloda)**
- **Mannitol**
- **Memantine HCL (Namenda)**
- **Neratinib (Nerlynx) and Capecitabine (Xeloda)**
- **Trastuzumab (Herceptin) given Intrathecally**
- **Trastuzumab emtansine (T-DM1; Kadcyla)**
- **Tucatinib (Tukysa)**

- **Abemaciclib (Verzenio)**: **Abemaciclib (Verzenio)** is a CDK4/6 inhibitor similar to the already FDA-approved drugs **palbociclib (Ibrance)** and **ribociclib (Kisqali)**. In Sept. 2017, it was approved as a second-line therapy in combination with **fulvestrant (Faslodex)** for hormone receptor-positive, HER2- postmenopausal patients whose first-line endocrine therapy failed. In Feb. 2018, **abemaciclib (Verzenio)** was approved in combination with an aromatase inhibitor as first-line therapy for hormone receptor-positive, HER2- postmenopausal MBC patients. **Abemaciclib (Verzenio)** is also approved alone (as a monotherapy) for hormone receptor-positive, HER2- postmenopausal patients whose first-line endocrine therapy failed and who also received prior chemotherapy that failed. A unique characteristic of **abemaciclib (Verzenio)** is its potential ability to cross the blood-brain barrier, making it a potentially attractive treatment option for brain metastasis. **From:** ***https://www.healio.com/hematology-oncology/breast-cancer/news/online/%7B48de16f7-6e3e-4440-b680-fce9166abf7c%7D/fda-expands-verzenio-approval-for-breast-cancer***

  A study of 52 evaluable HR+, HER2- MBC patients with brain metastasis who had received a median of 4 prior systemic therapies concluded that abemaciclib (Verzenio) can be beneficial for this population. 75% of the study participants had received chemotherapy, and 71% of patients had undergone prior endocrine therapy in the metastatic setting. 50% of the patients had received prior whole brain radiotherapy, 39% had stereotactic radiosurgery,

and 8% had undergone surgical resection. Abemaciclib (Verzenio) elicited a confirmed intracranial response in 6% of participants, and 38% of participants showed a decrease in the sum of their intracranial target lesions. The intracranial clinical benefit rate (consisting of complete response, partial response, or stable disease persisting for ≥ 6 months) was 25%, and the median progression-free survival was 4.4 months. **From:** ***https://meetinglibrary.asco.org/record/174775/abstract***

- **ANG1005:** This **paclitaxel (Taxol)-**like drug, which was studied in a clinical trial for MBC patients with brain metastasis, provided 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+ disease achieved stable disease. Among patients with leptomeningeal metastasis, the rate of 6-month overall survival was 63.6%. This drug is currently being tested in a Phase 3 trial (NCT03613181).
  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
- **Aprepitant (Emend)**: This is an anti-nausea drug that may help combat brain metastasis in addition to reducing nausea. In the laboratory (not human) setting, **aprepitant (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[115, PMID:24818961]: *http://www.sciencedaily.com/releases/2013/03/130319124221.htm***

- **Bevacuzumab (Avastin) and Irinotecan (CPT-11; Camptosar)** – *Not Yet FDA-Approved.* A very small study of four women with HER2+ brain metastasis who had failed other treatments and received **bevacizumab (Avastin)** and **irinotecan (CPT-11; Camptosar)** indicated that 100% of the patients had clinical response to treatment, and their median overall survival was 5 months longer than expected. **From[112, PMID:PMC4664841]: *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, BS could potentially be steroid-sparing for patients receiving brain irradiation. **From[113, 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 BS and found that 1,800 mg was comparable to half a dose of dexamethasone. So, she boosted her BS intake to two caplets 4 times a day during radiation and no longer needed to take any steroids. (Note: Patients interested in taking BS should confer with their doctor about dosage and frequency).

- **Chemotherapy Drugs:** Some studies have suggested that **capecitabine (Xeloda)**, high-dose **methotrexate,** the platinum

drugs **carboplatin** and **cisplatin**, **doxorubicin (Adriamycin)**, and **eribulin (Halaven)** can be effective in shrinking brain metastasis. **From:** ***https://meetinglibrary.asco.org/record/177605/abstract***

- **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[114, PMID:26374485]:** ***http://www.eurekalert.org/pub_releases/2015-10/osuw-ssn100615.php***

- **Entrectinib (Rozlytrek) for neurotrophic tropomyosin receptor kinase (*NTRK*) fusion-positive solid tumors:** In TRK fusion cancer, the *NTRK* gene fuses (joins) with an unrelated gene, causing overexpression of the TRK protein. Genomic alterations, such as *NTRK* gene fusions, are an ongoing area of focus in cancer research and treatment. In a basket trial, **entrectinib (Rozlytrek)** shrank tumors in 57.4% of people with *NTRK* fusion-positive solid tumors. Objective responses to **entrectinib (Rozlytrek)** were seen across 10 different solid tumor types (median duration of response was 10.4 months), including in people with and without central nervous system metastases at baseline. Importantly, **entrectinib (Rozlytrek)** shrank tumors that had spread to the brain in 54.5% of patients, with more than a quarter of these people having a complete response. Entrectinib has been FDA-approved for the treatment of *NTRK* fusion-positive, locally advanced or metastatic solid tumors in adult and pediatric patients who have either progressed following prior therapies or have no acceptable standard therapies. **From:** ***https://www.gene.com/media/press-releases/14759/2018-10-21/genentechs-investigational-personalized-***

- **Fam-trastuzumab deruxtecan-nxki (T-DXd; Enhertu):** This HER2-directed antibody-drug conjugate was FDA-approved in Dec. 2019 for the treatment of patients with unresectable or metastatic HER2+ breast cancer who have received at least one prior HER2-directed therapy. **Fam-trastuzumab deruxtecan-nxki (T-DXd; Enhertu)** was also approved in 2022 for HER2-low US patients who have had a prior chemotherapy and

in Jan. 2021 by the European Commission for HER2+ MBC patients who have received two or more prior anti-HER2 based regimens.
The ROSET-BM Study analyzed the outcomes of 104 HER2+ MBC patients with brain metastases (BM) and/or leptomeningeal metastases (LM) who were treated with **fam-trastuzumab deruxtecan-nxki (T-DXd; Enhertu).** Of the 104 patients, 70.2% had active BM, 16.3% had active BM and LM, 5.8% had stable BM, 1.9% had only LM, and 5.8% were not classified. Symptomatic BM were observed in 30.8% patients. The median number of prior lines of therapy was 4 (range, 1–15). The median duration of follow up from first **fam-trastuzumab deruxtecan-nxki (T-DXd; Enhertu)** treatment was 11.2 months. Results were highly encouraging: the overall response rate was 55.7%, the median progression-free survival was 16.1 months, and the median overall survival was not reached (overall survival at 1 year was 74.9%). From SABCS 2022 Poster Spotlight Discussion 7: Brain Metastases

As reported at ASCO 2024 (abstract #e13117), a single-institution, retrospective analysis of patients with MBC and brain metastases (HER2+, HER2-low, or HER2-) who received **fam-trastuzumab deruxtecan-nxki (T-DXd; Enhertu)** showed that the median overall survival was 65 weeks. Median central nervous system progression-free survival was the same for the HER2- low group compared to the entire study group.

- **Hormonal Therapies:** Hormonal therapies such as **tamoxifen (Nolvadex), letrozole (Femara), and megestrol acetate (Megace)** have been shown to be effective in treating breast cancer brain metastasis in some women with ER-positive tumors.

  In addition, continued endocrine therapy is associated with improved survival in hormone receptor-positive patients with breast cancer brain metastases. As per a review of 198 patients treated for ER-positive breast cancer brain metastases (BM) between 1990 and 2017 at an academic care center, 88 (44.4%) received endocrine therapy after the diagnosis of BM including **aromatase inhibitors (letrozole (Femara), anastrozole (Arimidex), or exemestane (Aromasin)), tamoxifen (Nolvadex), and fulvestrant (Faslodex).** The median overall survival (OS) was 15 months in the group that continued to receive endocrine therapy vs. 4 months in the group that did not. No significant OS

difference was observed among patients receiving **aromatase inhibitors, tamoxifen (Nolvadex), or fulvestrant (Faslodex).** In patients with concomitant leptomeningeal metastases (LM), endocrine therapy prolonged median OS significantly as well (7 months vs. 3 months). *<Author's note: It was unclear as to what, if any, treatments were taken in addition to endocrine therapies by patients with BM or LM>.* ***https://clincancerres.aacrjournals.org/content/early/2019/01/15/1078-0432.CCR-18-1968***

- **Lapatinib (Tykerb) and Capecitabine (Xeloda):** The studies that have explored the combination of **lapatinib (Tykerb)** are generally small in size, ranging from 13 to 138 patients. In nearly all studies, 85–100% of patients received prior **trastuzumab (Herceptin)** and whole brain radiotherapy (WBRT). Central nervous system (CNS) response ranged from 20 to 30%, which appears to be an improvement over responses observed with **lapatinib (Tykerb)** alone. One study addressed the role of the **lapatinib (Tykerb)** and **capecitabine (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 **trastuzumab (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 (Tykerb)** was also used in an experimental combination with **temozolamide (Temodar)** in a Phase 1 study of 16 HER2+ MBC patients with brain metastases, 14 of whom had been previously treated with WBRT. Of the 15 assessable patients, stable disease was achieved from the combination of **lapatinib (Tykerb)** and **temozolamide (Temodar)** in 10 patients (67%) and progression of disease in five patients (33%). **From[111, PMID:28177431; 118, 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:** ***https://www.ncbi.nlm.nih.gov/pubmed/7976640***

- **Memantine HCL (Namenda)** is an Alzheimer's drug that helps preserve cognitive skills after whole brain radiotherapy (WBRT).

In general study, patients treated with **memantine (Namenda)** had better cognitive function over time. Specifically, **memantine (Namenda)** delayed time to cognitive decline and reduced the rate of decline in memory, executive function, and processing speed in patients receiving WBRT. **From**: ***https://www.ncbi.nlm.nih.gov/pubmed/23956241***

- **Neratinib (Nerlynx) and Capecitabine (Xeloda) - Neratinib (Nerlynx)** is an orally ingested drug that crosses the blood-brain barrier (BBB), and in Feb. 2020 the FDA approved the combination of **neratinib (Nerlynx)** and **capecitabine (Xeloda)** for HER2+ MBC patients who had received 2 or more HER2-directed therapies in the metastatic setting. Approval was based upon results from the Phase 3 NALA trial, which showed that the combination of **neratinib (Nerlynx) and capecitabine (Xeloda)** reduced the risk of disease progression or death by 24% compared with **lapatinib (Tykerb)** plus **capecitabine (Xeloda).** Furthermore, the time to intervention for symptomatic central nervous system (CNS) disease was significantly delayed, with an overall cumulative incidence of 23% with **neratinib (Nerlynx)/lapatinib (Tykerb)** vs 29% with **lapatinib (Tykerb)/capecitabine (Xeloda).** In the Phase 2 TBCRC-022 trial, which enrolled 47 MBC patients with measurable, progressive, HER2+ brain metastases (92% after receiving CNS surgery and/or radiotherapy) who took **neratinib (Nerlynx) and capecitabine (Xeloda),** the results were compared between patients who previously took **lapatinib (Tykerb)** and those who did not. The median progression-free survival was 3.1 months among patients with prior **lapatinib (Tykerb)** exposure vs. 5.5 months for patients with no prior exposure, and the median overall survival was 15.1 months vs. 13.3 months respectively **From:** ***https://ascopost.com/issues/july-10-2019/nala-trial/*** and ***https://ascopubs.org/doi/10.1200/JCO.18.01511***

- **Trastuzumab (Herceptin) given Intrathecally (in the spinal canal)***:* Studies have shown that HER2+ patients treated with IV **trastuzumab (Herceptin)** have significantly lower concentrations of the drug in their cerebrospinal fluid than elsewhere in their bodies. This could explain the subsequent development of central nervous system (CNS) metastasis when non-CNS metastases are under control. Researchers hypothesized that the lack of efficacy of IV **trastuzumab (Herceptin)** with respect to brain metastasis in HER2-overexpressing breast cancers may result from a deficient

blood-brain barrier passage, and that intrathecal **trastuzumab (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 **trastuzumab (Herceptin)** concentration, she was still alive without treatment toxicity, and the progression of her brain and epidural metastasis had halted. **From[116, PMID:25547506]**

Trastuzumab (Herceptin) can also be combined with whole brain radiotherapy (WBRT), as per the results of a study of 31 patients presenting with HER2+ metastatic breast cancer in the brain and treated with WBRT and **trastuzumab (Herceptin).** After WBRT 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[111, PMID:28177431]**: ***https://academic.oup.com/annonc/article-lookup/doi/10.1093/annonc/mdw532***

- **Trastuzumab emtansine (T-DM1; Kadcyla) for pre-treated Asymptomatic HER2+ MBC:** One study indicated that patients with HER2+ MBC with pre-treated central nervous sytem metastasis and no symptoms who took **trastuzumab emtansine (T-DM1; Kadcyla)** experienced significantly longer overall survival than those assigned **capecitabine (Xeloda)** plus **lapatinib (Tykerb)**. **From[117, 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***

  Trastuzumab emtansine (T-DM1; Kadcyla) plus neratinib (Nerlynx): A Phase 2 study enrolled HER2+ MBC patients with measurable breast cancer brain metastases (BCBM) to receive **neratinib (Nerlynx)** 160 mg orally once daily plus **trastuzumab emtansine (T-DM1; Kadcyla)** 3.6 mg/kg IV every 21 days in three parallel-enrolling cohorts (groups). Cohort 4A enrolled patients with previously untreated brain metastases. Cohort 4B enrolled patients with BCBM progressing after prior local central nervous system (CNS)-directed therapy without prior exposure to **trastuzumab emtansine (T-DM1; Kadcyla).** Cohort 4C enrolled patients with BCBM progressing after prior local CNS-directed therapy who had previous exposure to **trastuzumab emtansine**

(T-DM1; Kadcyla). Among evaluable patients, CNS overall response rate in cohorts 4A (n=6), 4B (n=16), and 4C (n=21) was 50.0%, 25.0%, and 38.1% respectively. The overall survival at 12 months for cohorts 4A, 4B, and 4C was 83.3%, 86.2%, and 83.3% respectively. **From SABCS 2022 Poster Spotlight Discussion 7: Brain Metastases**

- **Tucatinib (Tukysa): Tucatinib (Tukysa)** in combination with **trastuzumab (Herceptin)** (or a biosimilar) and **capecitabine (Xeloda)** was FDA-approved in April 2020 for HER2+ MBC patients (with or without brain metastases) who have received at least one prior line of HER2-directed therapy in the metastatic setting. Approval was based upon the results of the HER2CLIMB clinical trial which enrolled 612 HER2+ MBC patients with or without brain metastases who had previously taken **trastuzumab (Herceptin), pertuzumab (Perjeta), and trastuzumab emtansine (T-DM1; Kadcyla).** Patients received either **tucatinib (Tukysa) + trastuzumab (Herceptin) + capecitabine (Xeloda), or trastuzumab (Herceptin) + capecitabine (Xeloda).** Among patients with brain metastases (40% of which were untreated, or treated and progressing), the progression-free survival (PFS) rate at 1 year was 24.9% in the **tucatinib (Tukysa)** arm vs. 0% in the **non-tucatinib (Tukysa)** arm, and the median PFS was 7.6 months vs. 5.4 months, respectively. At one year, the overall survival (OS) rate in the brain metastases population was 70.1% in the **tucatinib (Tukysa)** arm versus 46.7% in the **non-tucatinib (Tukysa)** arm (resulting in a 42% reduction in the risk of death), and the median OS was 18.1 months vs. 12.0 months respectively. **From:** ***https://www.esmo.org/Oncology-News/HER2CLIMB-and-DESTINY-Breast01-Findings-in-Heavily-Pretreated-HER2-positive-MBC*** and ***https://www.mdedge.com/hematology-oncology/article/214170/breast-cancer/tucatinib-called-game-changer-her2-positive*** and ***https://www.targetedonc.com/view/significant-delay-in-cns-progression-achieved-with-tucatinib-triplet-in-her2-metastatic-breast***
As presented at SABCS 2023 (GS01-10), the Phase 3 HER2CLIMB-02 trial (NCT03975647) enrolled 463 patients with locally advanced or metastatic HER2+ breast cancer, including 44% with brain metastases, to compare **tucatinib (Tukysa) + trastuzumab emtansine (T-DM1; Kadcyla)** versus placebo + **trastuzumab emtansine (T-DM1; Kadcyla).** The median time to disease progression or death in the **tucatinib (Tukysa) + trastuzumab emtansine (T-DM1; Kadcyla)** group was 9.5

months, and was 7.4 months in the **trastuzumab emtansine (T-DM1; Kadcyla)** only group. For only those patients with brain metastases, these times were 7.8 and 5.7 months, respectively. From: ***https://ascopost.com/news/december-2023/tucatinib-plus-t-dm1-may-benefit-patients-with-advanced-or-metastatic-her2-positive-breast-cancer/***

Clinical Trials: A list of Clinical Trials solely for brain metastasis is located at: ***https://mbcbrainmets.org/clinical-trials/***

A clinical trial for patients receiving WBRT 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[121, PMID:26296952]:** ***http://www.targetedonc.com/news/epigentic-targeted-agent-may-combat-resistance-in-many-cancers***

In this clinical trial specifically for patients undergoing WBRT, 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 WBRT will be more effective when combined with this experimental drug. **From:** ***https://www.clinicaltrials.gov/ct2/show/NCT02215512?term=rrx-001&rank=1***

Online support forums for those whose MBC has metastasized to the brain is available at: ***https://mbcbrainmets.org/resources/***

31. 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 (CSF) that flows through the meninges. About 2-5% 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 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+**
- **Triple-Positive MBC**
- **TNBC**
- **Patients with CK-19 mRNA-positive Circulating Tumor Cells** (CTCs)

From[50, PMID:25144278; 122, PMID:19228746; 123]: ***http://www.ascopost.com/issues/march-15,-2014/how-to-approach-the-problem-of-cns-metastasis-in-her2-positive-patients.aspx*** and ***https://vimeo.com/321238559/2e386b8fda***

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 CSF. 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.

LM can be difficult to diagnose. The most common method is by withdrawing CSF 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 LM. An MRI with gadolinium (a contrast agent) of the entire brain and spinal cord can also be used to diagnose LM and may be better than a CT scan. An MRI with a radioactive tracer can also be used to locate obstructions in the CSF or blood flow caused by LM. However, on an MRI, inflammatory disease or local infection can sometimes be mistaken for LM. ***https://mbcbrainmets.org/leptomeningeal-disease/***

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 ICP is elevated, radiation may be a way to relieve 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[124, 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 IT 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.

Patients with LM are encouraged to visit this comprehensive website called MBC Brain Mets that contains information about treatments for leptomeningeal disease, finding clinical trials, and more: ***https://mbcbrainmets.org/***

Drug Delivery options for leptomeningeal metastasis

Depending on the therapy, drug delivery may be provided as follows:

- **Intrathecally (IT)** directly into the CSF, usually via an Ommaya reservoir
- **Orally**
- **Through an IV port**

- **Intrathecally delivered drugs** are usually administered directly into the CSF 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. IT 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 CSF flow studies done before IT 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 IT chemotherapy, which is introduced directly into the CSF, 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 treatment options are varied and may include the following. Typically, **cytarabine (DepoCyt), trastuzumab (Herceptin), methotrexate, and thiotepa (Thioplex)** are the most commonly used drugs.

- **ANG1005** *(Not Yet FDA-Approved for MBC Patients)*
- **Capecitabine (Xeloda)**
- **Craniospinal Irradiation (CSI)**
- **Cytarabine (DepoCyt)**
- **Entrectinib (Rozlytrek) for *NTRK* fusion-positive solid tumors**
- **Fam-trastuzumab deruxtecan-nxki (T-DXd; Enhertu)** *(FDA-approved for HER2+ and HER2-low MBC Patients)*
- **Folinic acid (Leucovorin)**
- **Gemcitabine (Gemzar)**
- **Hormonal Therapies**
- **Methotrexate**
- **Radiation**
- **Thiotepa (Thioplex)** *(FDA-Approved for MBC Patients)*
- **Topotecan**
- **Trastuzumab (Herceptin), with or without lapatinib (Tykerb)**
- **Trastuzumab (Herceptin), tucatinib (Tukysa), and capecitabine (Xeloda)**
- **Whole Brain Radiotherapy (WBRT)**

- **ANG1005** *(Not Yet FDA-Approved for MBC Patients)*: This is a **paclitaxel (Taxol)-**like drug being studied to treat brain metastases and leptomeningeal metastases (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 (Taxol).** ANG1005 was shown to be generally safe and well-tolerated and demonstrated an adverse event profile consistent with conventional taxane therapy. **From[125]:** ***http://www.businesswire.com/news/home/20151120005128/en/Angiochem-Reports-Positive-Clinical-Data-ANG1005-Breast***

- **Capecitabine (Xeloda):** There have been some reports of a good response with this drug. **From:** ***https://pmc.ncbi.nlm.nih.gov/articles/PMC1871963/*** and ***https://ascopubs.org/doi/10.1200/JCO.2024.42.16_suppl.2018#:~:text=Background:%20Treatment%20options%20for%20patients,plus%20clinical%20signs/symptoms).***

- **Craniospinal Irradiation (CSI):** Full CSI 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[126, PMID:23593093]:** ***http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3625760/***

- **Cytarabine (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.

- **Entrectinib (Rozlytrek) for *NTRK* fusion-positive solid tumors:** In TRK fusion cancer, the neurotrophic tropomyosin receptor kinase (*NTRK*) gene fuses (joins) with an unrelated gene, causing overexpression of the TRK protein. Genomic alterations, such as *NTRK* gene fusions, are an ongoing area of focus in cancer research and treatment. In a basket trial, **entrectinib (Rozlytrek)** shrank tumors in 57.4% of people with *NTRK* fusion-positive solid tumors. Objective responses to **entrectinib (Rozlytrek)** were seen across 10 different solid tumor types (median duration of response was 10.4 months), including in people with and without central nervous system metastases at baseline. Importantly, **entrectinib (Rozlytrek)** shrank tumors that had spread to the brain in 54.5% of patients, with more than a quarter of these people having a

complete response. Entrectinib has been FDA-approved for the treatment of *NTRK* fusion-positive, locally advanced or metastatic solid tumors in adult and pediatric patients who have either progressed following prior therapies or have no acceptable standard therapies. **From:** ***https://www.gene.com/media/press-releases/14759/2018-10-21/genentechs-investigational-personalized-***

- **Fam-trastuzumab deruxtecan-nxki (T-DXd; Enhertu)** *(FDA-approved for HER2+ and HER2-low MBC Patients):* The ROSET-BM Study analyzed the outcomes of 104 HER2+ MBC patients with brain metastases (BM) and/or leptomeningeal metastases (LM) who were treated with **fam-trastuzumab deruxtecan-nxki (T-DXd; Enhertu)**. Of the 104 patients, 70.2% had active BM, 16.3% had active BM and LM, 5.8% had stable BM, 1.9% had only LM, and 5.8% were not classified. Symptomatic BM were observed in 30.8% patients. The median number of prior lines of therapy was 4 (range, 1–15). The median duration of follow up from first **fam-trastuzumab deruxtecan-nxki (T-DXd; Enhertu)** treatment was 11.2 months. Results were highly encouraging: the overall response rate was 55.7%, the median progression-free survival (PFS) was 16.1 months), and the median overall survival (OS) was not reached (OS at 1 year was 74.9%). In the 19 patients with LM, the 1-year PFS and OS were 60.7% and 87.1% respectively. **From SABCS 2022 Poster Spotlight Discussion 7: Brain Metastases**
  - **Folinic Acid (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***

- **Gemcitabine (Gemzar):** This is a commonly used chemotherapy drug for MBC, which may be helpful in cases of LM. **From[127, PMID:26279806]:** ***http://emedicine.medscape.com/article/1156338-treatment***

- **Hormonal Therapies:** There have been reports of good responses with **letrozole (Femara), anastrozole (Arimidex), or exemestane (Aromasin), megestrol acetate (Megace), and tamoxifen (Nolvadex).** Sometimes the drug may be administered intrathecally. **From[126, PMID:23593093; 129, PMID:15813508]:** ***http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3625760/***

In addition, continued endocrine therapy is associated with improved survival in hormone receptor-positive patients with breast cancer brain metastases. As per a review of 198 patients treated for ER-positive breast cancer brain metastases (BM) between 1990 and 2017 at an academic care center, 88 (44.4%) received endocrine therapy after the diagnosis of BM including **aromatase inhibitors (letrozole (Femara), anastrozole (Arimidex), or exemestane (Aromasin), tamoxifen (Nolvadex), and fulvestrant (Faslodex).** The median overall survival (OS) was 15 months in the group that continued to receive endocrine therapy vs. 4 months in the group that did not. No significant OS difference was observed among patients receiving **aromatase inhibitors, tamoxifen (Nolvadex), or fulvestrant (Faslodex).** In patients with concomitant leptomeningeal metastases (LM), endocrine therapy prolonged median OS significantly as well (7 months vs. 3 months). *<Author's note: It was unclear as to what, if any, treatments were taken in addition to endocrine therapies by patients with BM or LM>.* ***https://clincancerres.aacrjournals.org/content/early/2019/01/15/1078-0432.CCR-18-1968***

- **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[124, PMID:23593536]: ***http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3623833/***

- **Radiation:** It has been determined that LM patients who received proton therapy had a median progression-free survival of 7.5 months compared with 2.3 months for those receiving conventional radiation. Those who received proton therapy lived a median of 9.9 months, compared with just 6.0 months for those receiving conventional radiation. Side effects were similar between groups. **From:** ***https://www.mskcc.org/news/proton-therapy-leptomeningeal-metastasis-could-be-major-advance***

- **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[127, PMID:26279806]:** ***http://emedicine.medscape.com/article/1156338-treatment***

- **Topotecan:** A study of 31 MBC patients with LM were treated with intrathecal topotecan chemotherapy, 77% of whom also underwent systemic hormonal or chemotherapy. The median overall survival (OS) was 6.9 months, and patients remaining progression‑free during the first 4 to 6 weeks of therapy had a median OS of 11.5 months. **From:** ***https://onlinelibrary.wiley.com/doi/full/10.1002/cam4.3422?fbclid=IwAR2jk9p6ircNXt60gqaFsB9_O05CamGduqwKBnzyWQccN61ZMis2ir5Wxyc***
- **Trastuzumab (Herceptin)**: For women with HER2+ LM there is increasing and seemingly successful use of intrathecal **trastuzumab (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 (15-40 mg weekly) and high-dose (100-150 mg weekly) **trastuzumab (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 **trastuzumab (Herceptin)** and using steroids. Intrathecal **trastuzumab (Herceptin)** can also be delivered by lumbar puncture to the spinal cord. One woman survived 27 months after LM diagnosis. A complete leptomeningeal response, with no evidence LM at autopsy, was achieved after receiving 67 weekly administrations of intrathecal **trastuzumab (Herceptin)** with marked clinical improvement and no adverse events. In some cases, **trastuzumab (Herceptin)** may be combined with **lapatinib (Tykerb). From[128, PMID:21369716]:** ***http://www.ncbi.nlm.nih.gov/pubmed/21369716***
- **Trastuzumab (Herceptin), tucatinib (Tukysa), and capecitabine (Xeloda):** As per the TBCRC049 trial, HER2+ patients with leptomeningeal disease who took the combination of **tucatinib (Tukysa), capecitabine (Xeloda), and trastuzumab (Herceptin)** had a median overall survival (OS) of 10 months compared with an OS of 4 – 5 months for historical controls.
- **Whole Brain Radiotherapy (WBRT)**: 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 WBRT. Among the breast cancer patients, there was a 61% "crude" rate of stabilization or improvement of symptoms with WBRT. **From[126, PMID:23593093]:** ***http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3625760/***

Preservation of Memory with WBRT: As mentioned in the *Brain Metastasis* chapter, there is a type of WBRT 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. It can (and should) be combined with **memantine HCL (Namenda),** which is an Alzheimer's drug used to help preserve cognitive function. 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 WBRT without the hippocampus-sparing procedure. **From[109, PMID:25349290]:** ***https://vimeo.com/321234317/33959e4ee9***

One person wrote that his mother, who has HER2- 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. **Capecitabine (Xeloda)** was added after the 6th dose at 1500 mg in the morning and 1500 mg in the evening daily, and she continues to show a complete response.

Although somewhat dated, detailed information about potential therapies for LM can be found at **[130, PMID:9782234]**

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 cord 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, CSF 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 cerebrospinal 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+ 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."

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)

32. 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[131, 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[132, 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[133, 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[99, 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. For example, one patient with ascites claimed that the prescription diuretic drugs Lasix and Spironolactone helped her.

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***

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 it 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 may be 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 and 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:

Bevacizumab (Avastin) *(Not Yet FDA-Approved for MBC Patients)***:** In one study, nine patients with refractory malignant ascites were given **bevacizumab (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 (Avastin)** at 5 mg/kg monthly. Malignant ascites resolved without re-accumulating or repeat paracentesis in all nine patients after a single intraperitoneal dose of **bevacizumab (Avastin)** over a median observation period of over two months. **From[100]:** ***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. **Catumaxomab (Removab)** was evaluated as part of a Phase 1/2 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 IP infusions of **catumaxomab (Removab)** in doses of 10-200 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 (Removab)** 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[99, 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 (Removab)** led to a median interval of 15 days before a patient required an IP 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 (Removab)** can be administered in relatively frail outpatients, achieving good ascites control. A survival benefit was seen in fit patients who received complete IP **catumaxomab (Removab)** 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[102, 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 (Sandostatin LAR®)** arm and 17 to the control arm. The median time to next paracentesis was 28 and 14 days in the **octreotide (Sandostatin LAR®)** 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 (Sandostatin LAR®)-**treated patients described less abdominal bloating, abdominal discomfort, and shortness of breath at one month. As prescribed in this trial, **octreotide (Sandostatin LAR®)** did not seem effective in

prolonging the time to next paracentesis, although symptoms had improved. **From[103, 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 (Sandostatin LAR®)** (described above) in cases of malignant bowel obstruction, as well as in instances of trapped "loops" of bowel that are non-operable. **Octreotide (Sandostatin LAR®)** 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[104, PMID:22859627]: *http://www.cfp.ca/content/58/6/648.full***

33. 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 medical 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[134, 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 metastases 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 that 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 such as paclitaxel (Taxol or Abraxane) or docetaxel (Taxotere)),** hormonal and/or targeted therapy may sometimes be helpful against ocular metastasis.

From[134, PMID:23222564; 135, 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/***

34. 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, either alone or in combination with 5-FU or Imiquimod Cream**
- **Electrochemotherapy (ECT)**
- **Imiquimod Cream**
- **Medihoney**
- **Miltefosine (Miltex)**
- **Other:**
  - *Laser Ablation*
  - *Radiofrequency Ablation*
  - *Radiotherapy*
  - *Systemic therapy*
  - *Surgery*
- **REM-001 Therapy**
- **Silvasorb Gel**
- **Tucatinib (Tukysa)**
- **Xeroform Sterile Petrolatum Gauze Dressing**

- **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. Case accounts of three MBC patients with skin metastases who were treated with **cryotherapy in combination with either topical fluorouracil 5% (5-FU) or topical Imiquimod** revealed that all three patients had striking responses both locally and systemically. These unexpectedly favorable responses led the researchers to believe that treatment with cryotherapy and either topical 5-FU or Imiquimod is superior to cryotherapy alone, although further studies are warranted. **From:** ***https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6098206/***

- 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[136, 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[137, 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 **miltefosine (Miltex**) 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[138, 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%, and this therapy has received fast-track designation from the FDA. A new Phase 2 trial has begun for REM-001 (NCT05374915). **From:** ***https://breastcancer-news.com/2017/04/12/rem-001-benefits-most-women-with-skin-cancer-that-arises-from-breast-cancer/*** and ***https://www.targetedonc.com/view/rem-001-trial-begins-for-cutaneous-metastatic-breast-cancer-treatment***

- **Silvasorb Gel:** SilvaSorb Gel creates an antimicrobial barrier and is used for 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 metastasis to heal. She gently flushed the area with a mild saline solution, applied the Silvasorb, and covered it 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 (Tukysa):** In a very small study of 8 heavily pre-treated women with HER2+ skin metastasis, **tucatinib (Tukysa)** was combined with **capecitabine (Xeloda) and/or trastuzumab (Herceptin)** (an FDA-approved combination). 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. **From:** ***http://www.medicalnewstoday.com/articles/313476.php***

- **Xeroform Sterile Petrolatum Gauze Dressing:** Xeroform is a sterile wound dressing that won't stick to the wound, so dressing changes are less painful. Xeroform is also an "occlusive" dressing, which means the dressing prevents air from reaching the wound. An occlusive dressing will retain moisture, heat, and it will help the medication stay in place to promote a moist healing environment. Xeroform dressings are made of an absorbent fine mesh gauze that easily conforms to the body and feels comfortable and soothing against the skin. The fine mesh gauze has been combined with a 3% bismuth tribromophenate petroleum blend formula that provides bacteriostatic protection. Xeroform also deodorizes because it works to reduce wound odor. (*Author's note:* Several patients with cutaneous metastases claimed that this dressing substantially helped to reduce their discomfort).

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 that 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 effects, and 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[139, 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[140, 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[141, PMID:24832784]:** ***http://www.cochrane.org/CD003948/WOUNDS_topical-agents-and-dressings-for-fungating-wounds-ulcers-caused-by-cancer***

35. 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" receptors for estrogen, progesterone, and/or HER2/neu (sometimes referred to as ERBB2), and that there are currently therapies based on the presence or absence of these receptors.

The good news is that more potential targets for therapy are being discovered across all MBC subtypes, such as the androgen receptor, and the growth factor, FGFR1, which may signify resistance to hormonal therapy, and mutations. As of December 2024, there are multiple drugs in clinical trials targeting the above.

Research indicates that 88% of estrogen receptor-positive breast cancers, 50% of HER2+ breast cancers, and 25% of triple-negative breast cancers (TNBC) are androgen receptor (AR) positive. Although immunohistochemistry can be used to identify the AR, it is not widely done as there are currently no FDA approved anti-androgen drugs for MBC, and there is significant discrepancy in interpretation of expression of the AR.

Testing for FGFR1 overexpression can be done with a fluorescence in situ hybridization (FISH) test but testing for FGFR1 overexpression is not standard of care. The FGFR1 is also amplified in estrogen receptor-positive cancers and this is detected with standard DNA tests. However clinical trials have not found inhibitors of FGFR1 to be helpful for breast cancer treatment.

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+ MBC

Research and Potential Therapies for HER2- (or -Low) MBC

Research and Potential Therapies for Solely for TNBC

Research and Potential Therapies for Hormone Receptor-Positive, HER2+ MBC

Research and Potential Therapies 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

- **Aspirin (low-dose)**
- **Bisphosphonate Comparison of Zoledronic Acid (Zometa) vs. Denosumab (Xgeva)** *(Both FDA-approved)*
- **Capecitabine (Xeloda)** *(FDA-approved)*
- **Cell-Based Therapies**
- **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** *(Not Yet FDA-Approved for MBC Patients)*
- **Green Tea**
- **Melatonin**
- **Metformin**
- **Metronomic Chemotherapy**
- **Oral Paclitaxel (Taxol)** *(Not Yet FDA-Approved for MBC Patients)*
- **Pelareorep (Reolysin)** *(Not Yet FDA-Approved for MBC Patients, but has been accorded Fast-Track status)*
- **Saline-Based Adjuvant in Vaccines Increases Their Success**
- **Vitamin D Levels and Survival**

- **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 is associated with a reduced all-cause mortality by 47% and reduced 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. The design of the study did not allow determination of whether the aspirin was the cause of the mortality changes.

  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 that spread, but not in cancers that 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[143, PMID:24945997; 144, 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

Medivivor 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.

- **Bisphosphonate Comparison of Zoledronic Acid (Zometa) vs. Denosumab (Xgeva):** In a Phase 3 study of MBC patients with bone metastasis, **denosumab (Xgeva)** was superior to **zoledronic acid (Zometa)** in preventing skeletal-related events (SREs) such as fractures or the need for radiotherapy. **Denosumab (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%. Another study revealed that after 2 years, **denosumab (Xgeva)** improved bone density by 66% more than **zoledronic acid (Zometa).** Notably, 10% or more patients had a clinically meaningful improvement in health-related quality of life with **denosumab (Xgeva)** as compared to **zoledronic acid (Zometa).** However, **denosumab (Xgeva)** is associated with a higher risk of developing osteonecrosis of the jaw compared to **zoledronic acid (Zometa)**.
https://pmc.ncbi.nlm.nih.gov/articles/PMC7211372/#:~:text=reason%20for%20surgery.-,Conclusions,surgical%20procedures%20during%20active%20therapy. **From[146, PMID:22893628]:** ***http://clincancerres.aacrjournals.org/content/early/2012/08/01/1078-0432.CCR-11-3310.abstract*** and ***https://medivizor.com/view_article/43143360?id=33168***

- **Capecitabine (Xeloda):** The FDA-approved dosing schedule for capecitabine (Xeloda) is 1250 mg/m^2 twice daily for 14 days on followed by 7 days off. Tolerability and discontinuation are concerns with this dosing regimen. As reported at ASCO 2023 (abstract #1007), the X7-7 trial (NCT02595320), which enrolled patients with MBC (78% HR+ HER2-, 11% each HER2+ and triple negative), tested this dosing schedule compared with 1500 mg twice daily 7 days on 7 days off. No differences in progression-free survival or overall survival were found. Fewer patients in the 7 days on 7 days off arm experienced treatment discontinuation or grade 2-4 toxicity. From: Program Guide – ASCO Meeting Program Guide

- **Cell-based therapies.** Although no cell-based therapies are currently FDA approved for MBC, there is active research in this area. These therapies utilize cells of the immune system either directly or indirectly to help destroy cancer cells. Cell-based therapies may be useful in one or more subtypes of MBC. Examples of cell-based therapy include chimeric antigen receptor T-cells (CAR-T cells), natural killer (NK) cells, and Bria-IMT.
  CAR-T cells are approved for several types of blood cancers and are engineered for each individual patient. T cells, a type of immune cell important for killing tumor cells, are obtained from the patient's blood, modified to attack the cancer cells, grown in large numbers in the lab, and then injected back into the patient where the cells find and kill cancer cells. CAR-T cells engineered to find HER2-expressing MBC cells are being tested in clinical trials (for example, NCT03696030 and NCT06251544). From: https://www.cancer.gov/about-cancer/treatment/research/car-t-cells
  CAR NK cells are not patient specific. After undergoing 3 days of chemotherapy to get rid of immune cells that would destroy the CAR NK cells, the therapeutic cells are infused into the patient. In other cancer types, side effects are reported to be minimal and manageable, and the effect of the NK cells has so far lasted up to 1 year. Modified NK cells, chemotherapy, and targeted therapy are being tested in a Phase 1/2 trial (NCT06026657). From: ***https://www.mdanderson.org/cancerwise/car-nk-therapy-offers-new-treatment-option-for-blood-cancers.h00-159379578.html#:~:text=CAR%20NK%20cell%20therapy%20bolsters,cancer%20cells%20and%20attack%20them.***
  Bria-IMT is a cell-based therapy that when injected into a patient with breast cancer, stimulates the immune system to find and kill cancer cells. As reported at ASCO 2024 (abstracts #1022 and #e13119), a Phase 1/2 study (NCT03328026) showed that responses were seen in the brain and in patients who were resistant to antibody-drug conjugates. The side effects of this treatment include fatigue and injection-site reactions. A Phase 3 trial has begun (NCT06072612). At SABCS 2024, a poster (P5-10-12) was presented showing immunologically "cold" tumors could be turned "hot" with the combination of BRIA-IMT and an anti-PD1 checkpoint inhibitor, with an increase in anti-tumor CD8+ lymphocytes in the tumor microenvironment.
- **Diet and Exercise:** People with a history of early-stage breast cancer 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 longitudinal study from the Moores Cancer Center at the University of California San Diego. Although this study was done on early-stage breast cancer (not MBC) patients, there are ongoing trials in the metastatic setting (NCT05468034, NCT04354233, NCT03824145). **From[2, 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 [150, PMID:24451109]**
  Therefore, it may make sense to therapeutically target ARs in AR+ MBC in a similar manner as ERs are targeted in breast cancer. One AR blocking drug is **enzalutamide (Xtandi),** which - when combined with **fulvestrant (Faslodex)** - conferred a modest 25% clinical benefit rate at 6 months in a study of 32 HR+, HER2- MBC patients who had received a median of 2 prior lines of chemotherapy and 2 prior lines of endocrine therapy.
  As reported at SABCS 2023 (PO3-05-06), the ARIANNA trial, which was testing **enzalutamide (Xtandi)** + **exemestane (Aromasin)** was discontinued due to lack of efficacy. However, a trial of **enzalutamide (Xtandi)** alone or in combination with **mifepristone** (**Korlym**; a progesterone blocker) or chemotherapy is ongoing (NCT06099769), as well as trials of other anti-androgen agents (**bicalutamide (Cadodex)**, NCT06365788 and NCT05095207; **seviteronel**, NCT04947189; **vosilasarm/EP0062**, NCT05573126).

- **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 [151, 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.

A clinical trial (NCT03238196) for MBC patients whose MBC is hormone receptor positive, HER2-, and FGFR amplified is active but not recruiting. 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.

Rogaratinib is another FGFR inhibitor being studied; a trial in Spain (NCT04483505) was completed late 2023 but no results are published yet. Tasurgratinib is being evaluated in an ongoing trial (NCT04572295), and a poster on biomarker assessment to predict sensitivity to the drug was presented at SABCS 2024 (P4-10-18).

- **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+ 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 epigallocatechin gallate (EGCG), which are catechins (anti-oxidants) that are found in green tea.

  The article cites green tea's applications to the following:

  HER2+ 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 (Nolvadex)** in the treatment of ER-positive and ER-negative breast cancers.

  *Overcoming **Tamoxifen (Nolvadex)**/SERM Resistance:* Even in cases of **tamoxifen (Nolvadex)-**resistant breast cancer, administering green tea catechins with **tamoxifen (Nolvadex)** has been reported to reverse **tamoxifen (Nolvadex)** resistance.

Mitigating Resistance to Chemotherapy: Finally, it has been shown that green tea micronutrients may be helpful in reducing resistance to chemotherapy.

Although these findings are interesting, the concentrations used in the laboratory would be difficult to achieve by actually drinking green tea, and it may be unsafe to attempt to drink large amounts. Smaller amounts of a few cups a day or less are safe but less likely to have important biological effects on cancer.

(As an aside, there has been no evidence of interaction between green tea catechins and aromatase inhibitors). **From[154, PMID:25471334]:**
https://www.ncbi.nlm.nih.gov/pubmed/25471334

- **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 [156, 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[157, PMID:PMC2033724]:** ***https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2033724/***

There are no current trials studying the efficacy of melatonin in MBC.

- **Metformin (Glucophage):** The diabetes drug **metformin (Glucophage)** 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 (Glucophage)** has emerged as a potential anticancer agent. Epidemiological, preclinical, and clinical evidence supports the use of **metformin (Glucophage)** as a cancer therapy. The ability of **metformin (Glucophage)** 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 (Glucophage)** may exhibit direct inhibitory effects on cancer cells by inhibiting mammalian target of **rapamycin (mTOR)** signaling and protein synthesis. Presentations at SABCS 2023 (PO1-05-11 and PO2-08-06) showed that overall survival was longer in people with de novo MBC who took metformin (Glucophage) plus chemotherapy compared to chemotherapy alone (5-year OS 21.2% vs 5.6%). **Metformin (Glucophage)** may change the tumor microenvironment from pro- to anti-tumorigenic (at least in early-stage breast cancer). **From[159, PMID:21470407]:** ***http://www.biomedcentral.com/1741-7015/9/33***

  In a human study that analyzed the effect of **metformin (Glucophage)** 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 (Glucophage)** before their diagnosis, and 97 reported

use of the drug after diagnosis. Results of the study showed that the patients who used **metformin (Glucophage)** 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 (Glucophage)** after their cancer diagnosis were almost 50% more likely to survive than non-users. This analysis concludes that use and efficacy of **metformin (Glucophage)** is time-dependent (i.e. whether it is taken before vs. after diagnosis). **From[160]:**
http://medicalxpress.com/news/2016-06-diabetes-drug-metformin-cancer-treatment.html

Clinical trials of **metformin (Glucophage)** in MBC have been mixed at best, with most NOT showing an improvement in progression-free survival or overall survival.

- **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. However, the design of this study is subject to bias. **From [161, PMID:24649151]:**
http://www.pubfacts.com/detail/24649151/Metronomic-chemotherapy-for-metastatic-breast-cancer-to-prolong-time-to-treatment-failure-to-12-mont
The concept of metronomic therapy was not supported in prospective studies in breast cancer and other cancers and was largely abandoned along with anti-angiogenic therapies.

- **Oral Paclitaxel (Taxol)** *(Not Yet FDA-Approved for MBC Patients):* According to a Phase 3 clinical trial of 402 MBC patients that compared an oral formulation of the chemotherapy drug **paclitaxel (Taxol)** with the current FDA-approved intravenous (IV) form, the oral version elicited a better response and increased survival. Results indicated that 40.4% of patients on the oral formulation (consisting of oral **paclitaxel (Taxol)** and encequidar, which increases drug bioavailability) had a confirmed tumor response, compared with 25.5% in the IV group. Furthermore, median overall survival was 27.9 months for the oral group compared with 16.9 months for the IV group. Importantly, the incidence of neuropathy was 17% in the oral group compared with 57% in the IV group, and there was a lower level of severity when it occurred. Hair loss (alopecia) was also reduced in the oral group. Conversely, neutropenia (low neutrophil white blood count), infection, and gastrointestinal side effects were higher in the oral group, although these symptoms were generally low grade.
https://ascopubs.org/doi/full/10.1200/JCO.21.02953

- **Pelareorep (Reolysin)** *(Not Yet FDA-Approved for MBC Patients, but has been accorded Fast Track status):* **Pelareorep (Reolysin)** is a virus that preferentially enters and kills cancer cells. This leaves debris that activates the immune system, leaving the tumor "inflamed" and more likely to be recognized and killed by the immune system. A combination of **pelareorep (Reolysin)** and the chemotherapy paclitaxel (Taxol) was tested in the Phase 2 IND.213 trial (NCT01656538) and the Phase 2 BRACELET-1 trial

(NCT04215146). In IND.213, in which the breast cancer subtype was not specified, although progression-free survival (PFS) was not different between the two groups, overall survival was 17.4 months with the combination and 10.4 months in the paclitaxel (Taxol)-only group. As reported at ASCO 2023, in BRACELET-1, which enrolled HR+, HER2- MBC patients, median PFS was 6.4 months with **paclitaxel (Taxol)** alone and 9.6 months with the combination. In May 2017, **pelareorep (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. This treatment is likely moving forward to a Phase 3 trial in combination with paclitaxel (Abraxane). ***https://www.prnewswire.com/news-releases/oncolytics-biotech-advances-toward-registration-enabling-trial-for-pelareorep-in-breast-cancer-with-submission-of-type-c-meeting-request-to-fda-302113665.html*** Also a Phase 2 trial is ongoing for metastatic TNBC. ***https://www.cancer.gov/research/participate/clinical-trials-search/v?id=NCI-2020-02940*** **From:** ***https://www.adlainortye.com/upload/2022/12/05/16702308665388exmme.pdf*** and ***https://ascopubs.org/doi/10.1200/JCO.2023.41.16_suppl.1012*** and ***https://oncolyticsbiotech.com/press_releases/oncolytics-biotech-advances-toward-registration-enabling-trial-for-pelareorep-in-breast-cancer-with-submission-of-type-c-meeting-request-to-fda-2/***

- **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 was added to the saline/peptide vaccine, which produced a strong T-cell response.
A comparison of **saline/peptide vs. IFA/peptide** 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 [162, PMID:23455713]:** ***http://www.mdanderson.org/newsroom/news-releases/2013/cancer-vaccines-channel-immune-attack-to-injection-site.html***

- **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 [165, 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 [166, PMID:24463450]**

Research and Potential Therapies for Hormone Receptor-Positive MBC

Hormone receptor positive MBC patients are encouraged to read the section entitled, *"Research and Potential Therapies for HER2- (or Low) MBC"* since the studies or drugs therein may be applicable.

- **AC699**
- **Alisertib (MLN8237)** *(Not Yet FDA-Approved for MBC Patients)*
- **Alpelisib (Piqray)** *(FDA-Approved for MBC Patients)*
- **Anastrozole (Arimidex) and Fulvestrant (Faslodex)**
- **Atezolizumab**
- **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
- **Camizestrant (AZD9833)** (an oral SERD) **with and without Ibrance (Palbociclib)** *(Not Yet FDA-Approved for MBC Patients)*
- **Capivasertib (Truqap)** *(FDA-Approved for MBC Patients)*
- **Datopotamab deruxtecan (Dato-DXd; Datroway)**
- **Eftilagimod Alpha** *(Not Yet Approved for MBC Patients)*
- **Elacestrant (Orserdu)** *(Approved for MBC Patients)*
- **Endoxifen (or Z-Endoxifen) for ER+ MBC**, Including Hormone Therapy Resistant Breast Cancer *(Not Yet FDA-Approved for MBC Patients)*
- **Enobosarm** *(Not Yet FDA-Approved for MBC Patients)*
- **Fam-trastuzumab deruxtecan-nxki (T-DXd; Enhertu)**
- **Giredestran**t *(Not Yet FDA-Approved for MBC Patients)*
- **Inavolisib (Itovebi)** *(FDA-Approved for MBC patients)*
- **Lenvatinib (Lenvima) and Letrozole (Femara)** *(Lenvatinib is Not Yet FDA-Approved for MBC Patients)*
- **Neratinib (Nerlynx) plus Trastuzumab (Herceptin) plus Fulvestrant (Faslodex)**
- **Palazestrant** *(Not Yet FDA-Approved for MBC Patients)*
- **Pembrolizumab (Keytruda)**
- **PF-07248144**
- **Re-Trying Hormonal Therapies**
- **Samuraciclib (CT-7001)** *(Not Yet FDA-Approved for MBC Patients)*
- **SARMs (Selective Androgen Receptor Modulators)** *(Not Yet FDA-Approved for MBC Patients):*

- **SERCAs (Selective Estrogen Receptor Covalent Antagonists)** *(Not Yet FDA-Approved for MBC Patients)*
- **ShERPAs (Selective human Estrogen Receptor Partial Agonists)** *(Not Yet FDA-Approved for MBC Patients)*
- **Tamoxifen (Nolvadex) Resistance and Toremifene (Fareston)**
- **Testosterone Propionate Study**
- **Vepdegestrant (ARV-471)** *(Not Yet FDA-Approved for MBC Patients)*
- **ZN-c5** (*Not Yet FDA-Approved for MBC Patients*

- **AC699.** As reported at ASCO 2024 (abstract #3074), AC699, a novel estrogen receptor degrader, is being studied in a Phase 1 trial (NCT05654532). Twenty-one patients with ER+/HER2- MBC who had received at least one prior line of therapy were enrolled. 21% of patients (4/19) had either a complete or partial response, and 19% (6/21) had a complete or partial response or stable disease. Of those with an *ESR1* mutation (9), a higher percent had a complete or partial response (50%), and one more had a stable response (56% total). AC699 was granted fast track status in August 2024.

- **Alisertib (MLN8237)** *(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. A Phase 2 randomized clinical trial (NCT02860000) studied **alisertib** with or without **fulvestrant (Faslodex)** in 91 patients with hormone therapy-resistant, HER2- MBC. There was no difference between **alisertib** alone and when combined with **fulvestrant (Faslodex).** Median progression-free survival (PFS) time was 5.4 months with both drugs. Thus, adding **fulvestrant (Faslodex)** did not improve PFS. NCT06369285 is another Phase 2 trial of alisertib in combination with endocrine therapy that has recently opened. **From [167]: *http://cancerres.aacrjournals.org/content/72/24_Supplement/P6-10-02.short*** and ***https://pubmed.ncbi.nlm.nih.gov/36892847/ and https://www.onclive.com/view/aurka-pathway-gains-ground-as-targetable-option-in-metastatic-breast-cancer***

- **Alpelisib (Piqray).** The oral PI3K inhibitor, **alpelisib (Piqray),** is FDA-approved for MBC patients with *PIK3CA* mutations and continues to be tested with hormone therapy in a Phase 2 trial (NCT04762979) and in a Phase 1 trial in combination with sacituzumab govitecan (Trodelvy; ASSET; NCT05143229).

- **Anastrozole (Arimidex) and Fulvestrant (Faslodex)**: A recent study reported that hormone receptor-positive, HER2- MBC patients taking **anastrozole (Arimidex)** and **fulvestrant (Faslodex)** had a median overall survival (OS) of 49.8 months (as opposed to 42 months in the **anastrozole (Arimidex)-**only arm), which is the longest ever reported for this type of patient. Progression-free survival (PFS) in the combination arm was 15 months vs. 13.5 months in the **anastrozole (Arimidex)-**only arm. Among women who had no prior **tamoxifen (Nolvadex)** use, median OS was 52.2 months in the combination arm and 40.3 months in the **anastrozole (Arimidex)**-only arm, and median PFS was 16.7 months vs. 12.7 months respectively. Among women who had received **tamoxifen (Nolvadex)** previously, median OS was 48.2 months in the combination arm vs. 43.5 months in the **anastrozole (Arimidex)**-only arm, and median PFS was 13.9 months vs. 13.6 months respectively. The **fulvestrant (Faslodex)** dosage used in the study was 250 mg per month after the first loading dose (as compared to the usual 500 mg per month dosage). There is a recruiting trial of **anastrozole (Arimidex)**, **fulvestrant (Faslodex)**, and **abemaciclib (Verzenio)** (NCT05524584). **From:** ***https://www.healio.com/hematology-oncology/breast-cancer/news/online/%7Bb6232f6b-4a1b-4892-9bcd-0a58048372b6%7D/anti-estrogen-drug-combination-confers-durable-survival-benefit-in-breast-cancer-subset***

- **Atezolizumab**: As reported at SABCS 2023 (PS12-08), atezolizumab has been tested in patients with HR+ MBC. At the 24–week interim analysis of the MORPHEUS HR+ BC study (NCT03280563), which tested atezolizumab plus fulvestrant (Faslodex) with or without **abemaciclib (Verzenio)**, median progression-free survival was 6.34 months for atezolizumab plus **fulvestrant (Faslodex)** with **abemaciclib (Verzenio)** compared with 3.15 months with **atezolizumab plus fulvestrant (Faslodex)** and 1.95 months with **fulvestrant (Faslodex)** only.
- **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 two-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 (Nolvadex)** and/or to aromatase inhibitors. As of December 2024, there are no ongoing trials in the US, and it does not appear that results of a trial in combination with palbociclib, completed in 2022, have been published. **From [168, 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 **fulvestrant (Faslodex)** — versus **fulvestrant (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. **Fulvestrant (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 **fulvestrant (Faslodex)**. The study results also suggest that the drug combination can delay or overcome resistance to **fulvestrant (Faslodex)**. As of December 2024, bortezomib may not be moving forward in ER+ MBC. There are no ongoing trials, and results in prior trials were not

encouraging. **From [169, PMID:28721390]: *http://medicine.yale.edu/news/article.aspx?id=8462***

- **Camizestrant (***(Not Yet FDA-Approved for MBC Patients):* A Phase 1 study called SERENA-1 enrolled 146 hormone receptor-positive, HER2- MBC patients to evaluate AZD9833 in combination with palbociclib (Ibrance) and as a monotherapy. The median number of prior treatments for the 98 patients in the monotherapy arm was 3, and the median number of prior treatments for the 48 patients in the combination arm was 2. In the monotherapy arm, 53% of patients had received prior fulvestrant (Faslodex), and 62% had taken a prior CDK4/6 inhibitor. In the combination arm, 58% of patients had received prior fulvestrant (Faslodex), and 69% had taken a prior CDK4/6 inhibitor. The clinical benefit rate was 36% for patients in the monotherapy arm and 50% in the combination arm. Camizestrant is an oral SERD that the randomized Phase 2 SERENA-2 trial compared with **fulvestrant (Faslodex)** in 240 women with locally advanced or metastatic ER-positive, HER2- breast cancer who previously received endocrine therapy for advanced disease. Results showed median progression-free survival (PFS) of 7.2 to 7.7 months with camizestrant and 3.7 months with **fulvestrant (Faslodex)**. Among those with *ESR1* mutations, results showed median PFS of 6.3 months to 9.2 months with camizestrant vs. 2.2 months with **fulvestrant (Faslodex).** Results from the SERENA-1 trial of **camizestrant** in combination with **ribociclib (Kisqali)** in a heavily pretreated population presented in a poster at SABCS 2024 (PS7-08) showed median PFS of 8.1 months at data cut-off. SERENA-6 is an ongoing trial of camizestrant + CDK4/6 inhibitor vs aromatase inhibitor + CDK4/6 inhibitor (NCT04964934). **From:** ***https://www.healio.com/news/hematology-oncology/20221208/camizestrant-extends-pfs-for-postmenopausal-women-with-advanced-breast-cancer***

- **Capivasertib (Truqap).** The AKT inhibitor, **capivasertib (Truqap)**, is FDA-approved for MBC patients with alterations in the genes *PIK3CA*, *AKT1*, and/or *PTEN* and continues to be tested with **fulvestrant (Faslodex)** and a CDK4/6 inhibitor in a Phase 3 trial (CAPItello-292; NCT04862663).

- **Datopotamab deruxtecan (Datroway)**: **Datopotamab deruxtecan (Dato-DXd; Datroway)** is an antibody-drug conjugate (ADC) that was studied in the TROPION-Breast01

Phase 3 Trial (NCT05104866) in 732 patients with hormone receptor-positive, HER2- (HR+/HER2–) MBC with 1–2 prior lines of systemic chemotherapy. The median progression-free survival (PFS) was 6.9 months with **datopotamab deruxtecan (Dato-DXd; Datroway)** and 4.5 months with chemotherapy. **Datopotamab deruxtecan (Dato-DXd; Datroway)** was also associated with an improved PFS in those who had received prior CDK4/6 inhibitor treatment. **Datopotamab deruxtecan (Dato-DXd; Datroway)** delayed time to the next therapy and a decrease in quality of life. **Datopotamab deruxtecan (Dato-DXd; Datroway)** has also been studied in the Phase 1 TROPION-PanTumor01 (NCT03401385) trial; PFS was 8.3 months in HR+/HER2- patients with MBC. A trial for **datopotamab deruxtecan (Dato-DXd; Datroway)** for patients with brain metastatses, including ER+ MBC, is recruiting (NCT06176261). From: Abstract GS02-01 at SABCS 2023, ***https://www.cancertherapyadvisor.com/reports/dato-dxd-new-treatment-option-hr-her2-advanced-breast-cancer/*** and ***https://ascopubs.org/doi/10.1200/JCO.23.01909***

- **Eftilagimod Alpha** *(Not Yet Approved for MBC Patients)* in combination with paclitaxel (Taxol): The Phase 2b IMP321-P011 trial of 227 patients with HR+, HER2- endocrine therapy-resistant disease determined that the combination of the immunotherapy drug **eftilagimod alpha** (given via subcutaneous injection) with **paclitaxel (Taxol)** produced a modest increase in median overall survival (OS). The effects were more significant in patients younger than 65 years old, had low monocytes, or had more aggressive disease (luminal B). Overall, the median OS was 20.4 months in patients receiving the combination vs 17.5 months in those who received **paclitaxel (Taxol)** alone. For patients under the age of 65 receiving the combination, the median OS was 22.3 months compared with 14.8 months for **paclitaxel (Taxol)** alone. For patients with low monocytes who received the combination, the median OS was 32.5 months vs 12.9 months for **paclitaxel (Taxol)** alone. And for patients with luminal B MBC, the median OS for the combination was 16.8 months vs 12.6 months for **paclitaxel (Taxol)** alone. From: ***https://www.onclive.com/view/eftilagimod-alpha-paclitaxel-combo-shows-improved-os-in-metastatic-hr-breast-cancer-subsets***
- **Elacestrant (Orserdu).** The oral selective estrogen receptor degrader (SERD), **elacestrant (Orserdu)** is FDA-approved for MBC patients with an *ESR1* mutation and continues to be

investigated in combination with other treatments in a Phase 1b/2 trial (ELEVATE; NCT05563220) and in comparison with hormone therapy in a Phase 3 (ELEGANT; NCT06492616).

- **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 (Nolvadex)**, 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 (Nolvadex)** and aromatase inhibitors. There were up to 60-fold higher levels of endoxifen compared to endoxifen levels achieved with the standard dose of **tamoxifen (Nolvadex)**, 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, **fulvestrant (Faslodex)**, and **tamoxifen (Nolvadex)**. This drug is also effective for patients with CYP2D6 metabolism issues who are not able to benefit from **tamoxifen (Nolvadex)**. A trial testing endoxifen (EVANGELINE; NCT05607004) opened in late 2023. No updates are available as of December 2024. **From[175, PMID:PMC5648176]:** ***https://www.sciencedaily.com/releases/2013/12/131212185835.htm*** and ***https://www.sciencedaily.com/releases/2017/08/170830202125.htm***

- **Enobosarm** *(Not Yet FDA-Approved for MBC Patients):* Enobosarm is a first-in-class, oral nonsteroidal androgen receptor (AR) agonist designed to treat patients with AR-positive, ER-positive advanced breast cancer. Findings from the Phase 2 G200802 (NCT02463032) trial determined that **enobosarm** elicited a clinical benefit rate (CBR) of 32%. Patients who had greater than 40% AR staining experienced an overall response rate (ORR) of 50% and a CBR of 79%, but patients with an AR staining of less than 40% experienced an ORR of 0% and a CBR of 18%, indicating that AR expression may be a useful biomarker of response for treatment selection. The Phase 3 ARTEST study (NCT04869943) (SABCS 2023 PO2-27-03) was discontinued for administrative reasons not related to safety or efficacy. The Phase 3

ENABLAR-2 study (NCT05065411), originally presented at SABCS 2023 (PO4-27-06) has been terminated, and there are no ongoing trials of **enoborsarm** as of December 2024. **From:** ***https://www.onclive.com/view/schwartzberg-on-bringing-seminal-observations-on-ar-from-bench-to-bedside-in-er-breast-cancer*** and ***https://www.practiceupdate.com/C/162274/56?elsca1=emc_enews_topic-alert*** and ***https://www.practiceupdate.com/c/162877/2/1/?elsca1=emc_enews_daily-digest&elsca2=email&elsca3=practiceupdate_onc&elsca4=oncology&elsca5=newsletter&rid=NTQ3NDQ1MTI3NDI5S0&lid=20844069*** and ***https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(24)00004-4/fulltext***

- **Fam-trastuzumab deruxtecan-nxki (T-DXd; Enhertu).** This drug is FDA approved for HER2+, HER2-low, and HER2-ultralow MBC after progression on endocrine therapy. The Phase 1b trial Destiny-Breast08 (NCT04556773) is testing **trastuzumab deruxtecan (T-DXd; Enhertu)** + **fulvestrant (Faslodex) or anastrozole (Arimidex)** in patients with HR+ HER2-low MBC. Results presented at SABCS 2023 (RF02-03) show that the median progression-free survival was 13.4 months in the **trastuzumab deruxtecan (T-DXd; Enhertu)** + **anastrozole (Arimidex)** arm and not estimable in the **trastuzumab deruxtecan (T-DXd; Enhertu) + fulvestrant (Faslodex)** arm. Destiny-Breast06 demonstrated a benefit of T-DXd after endocrine therapy as the first-line chemotherapy for HER2-low and HER2-ultralow ER+ breast cancer. From: ***https://www.nejm.org/doi/abs/10.1056/NEJMoa2407086*** and ***https://ascopubs.org/doi/10.1200/JCO.2024.42.17_suppl.LBA1000*** and ***https://www.medpagetoday.com/hematologyoncology/breastcancer/113982?xid=nl_mpt_DHE_2025-01-28&mh=a5b163f9bc8ee8a077e31262b4e7fbea&zdee=gAAAAABm4uO7C7ZaFGb-lPkv0XjdXPudJVqo8AKQVbmnDdExKpj1FRqIByijunUeZWaP0WGnNfVuYc5IhvmduVfuvx40EIVkpXfRiiie6AGLsf0JbXchHPY%3D&utm_source=Sailthru&utm_medium=email&utm_campaign=Daily%20Headlines%20Evening%20-%20Randomized%202025-01-28&utm_term=NL_Daily_DHE_dual-gmail-definition***

- **Giredestrant** *(Not Yet FDA-Approved for MBC Patients):* **Giredestrant** is an oral, non-steroidal, selective ER antagonist with promising single-agent activity based upon the results of a Phase 1 trial (NCT03332797) of 111 patients with HR+, HER2- locally advanced breast cancer or MBC. All patients had breast cancer that progressed while receiving endocrine therapy. **Giredestrant** exhibited antitumor activity across all patient subgroups, regardless of *ESR1* mutation status or prior treatment with CDK4/6 inhibitors, **fulvestrant (Faslodex)**, or chemotherapy. As reported at SABCS 2023 (PO1-05-07) and in a recent publication, a Phase 2 study (NCT04576455) showed that as second- or third-line treatment in patients with ER+ MBC, **giredestrant** had greatest benefit in patients with *ESR1* mutations, with specific *ESR1* mutations associated with greater response to giredestrant. In addition (SABCS 2023 PS17-07), interim analysis of the MORPHEUS BC trial (NCT04802759) in patients with MBC with a *PIK3CA* mutation and 1-2 prior lines of endocrine therapy showed that the median progression-free survival with addition of **inavolisib (Itovebi)** to **giredestrant** was 10.3 months. **Giredestrant** continues to be tested in a Phase 2 trial (NCT05708235; SABCS 2023 PO1-20-02). **From:** ***https://theoncologist.onlinelibrary.wiley.com/doi/full/10.1002/onco.13874?elq_cid=25966017&elq_mid=54046&fbclid=IwAR0yxu7v7q4XN6UUOxunbrA5LhQ-MoN49t6Ao6JF8cJZESsORNh3P8R3QhI&utm_campaign=34397&utm_content=Email-Research-DirectEmal_ONCO_Conf.persp_ASCO_2021-07-02&utm_medium=email&utm_source=eloquaEmail#.YObnzZbqbqc.facebook*** and ***https://synopsi.medpagetoday.com/article/316474/giredestrant-for-estrogen-receptor-positive-her2-negative-previously?xid=nl_mpt_Oncology_update_2024-03-29&mh=a5b163f9bc8ee8a077e31262b4e7fbea&utm_source=Sailthru&utm_medium=email&utm_campaign=Automated%20Sp***

- **Inavolisib (Itovebi)**. The PIK3CA inhibitor, **inavolisib (Itovebi)**, is FDA-approved for MBC patients and continues to be investigated in two Phase 3 clinical trials: INAVO121 (NCT05646862) and INAVO122 (NCT05894239). The INAVO121 study is evaluating **inavolisib (Itovebi)** plus **fulvestrant (Faslodex)** compared with **alpelisib (Piqray)** plus **fulvestrant (Faslodex)** in patients with HR+, *PIK3CA*-mutant advanced or metastatic breast cancer who experienced disease progression during or after treatment with a CDK4/6 inhibitor. As

of SABCS 2023 (PO2-19-08), enrollment has just begun (four patients). The INAVO122 study is evaluating **inavolisib (Itovebi)** plus **pertuzumab/trastuzumab/hyaluronidase (Phesgo)** compared with **Phesgo** plus a taxane in patients with HER2+ MBC as first-line therapy in the metastatic setting. However, there remains controversy whether to give this agent in the first-line metastatic setting due to additional toxicity, such as hyperglycemia, or to reserve PIK3CA-targeted therapy for a later line of treatment.

- **Lenvatinib (Lenvima)** *(Not Yet FDA-Approved for MBC Patients):* **Lenvatinib (Lenvima)**, an approved drug that is used to treat liver, thyroid, and kidney cancer, is currently being studied in other types of cancer. It works by inhibiting vascular endothelial growth factor (VEGF), which is a signal protein produced by cells that stimulates the formation of blood vessels that in turn promote tumor growth. In the Phase 2 dose expansion cohort (NCT02562118) that included 31 ER+, HER2- MBC patients with a median of 5 lines of therapy, **lenvatinib (Lenvima)** conferred a 1-year overall survival rate of 59.7%. In the subgroup of patients who were resistant to CDK4/6 inhibitors, the median progression-free survival was 6.2 months, and the 1-year overall survival rate was 62.4%. **From:** ***https://aacrjournals.org/clincancerres/article/28/11/2248/698933/Phase-Ib-II-Dose-Expansion-Study-of-Lenvatinib*** and ***https://meetinglibrary.asco.org/record/175824/abstract***
  Lenvatinib (Lenvima) is also being studied in combination with **pembrolizumab (Keytruda)**. A Phase Ib/II trial (NCT06110793) is testing **lenvatinib (Lenvima)** plus **pembrolizumab (Keytruda)** plus **fulvestrant (Faslodex)** in ER+ HER2- MBC. A Phase II trial (NCT05286437) is testing **lenvatinib (Lenvima)**, **pembrolizumab (Keytruda)**, and **letrozole (Femara)** in advanced, endocrine-resistant breast cancer (SABCS 2024 P2-08-29). This trial is only open in Singapore.

- **Neratinib (Nerlynx) plus Trastuzumab (Herceptin) plus Fulvestrant (Faslodex):** In the Phase 2 SUMMIT trial (NCT01953926), which included 33 patients with HR+, HER2-, *HER2*-mutated MBC who had previously received CDK4/6 inhibitors, the triplet regimen of **neratinib (Nerlynx), fulvestrant (Faslodex),** and **trastuzumab (Herceptin)** induced an objective response rate of 42.4%. The median duration of response was 14.4 months, and the median progression-free survival (PFS) was 7.0

months. This trial has since been terminated. As reported at SABCS 2023 (PO3-05-07), in the Phase 2 SOLTI-1718 NEREA trial (NCT04460430), which tested **neratinib (Nerlynx)** and hormone therapy in patients with HR+/HER2-, PAM50 HER2-enriched advanced breast cancer, early results showed that PFS at 6 months occurred in 1 patient, median PFS was 1.7 months, and 11 of 12 patients had discontinued treatment (9 due to progressive disease and 2 due to toxicity). The authors noted a lack of efficacy for this combination, and this trial has been terminated. **From:** ***https://www.cancernetwork.com/view/neratinib-combo-yields-positive-orr-in-her2-mutant-metastatic-breast-cancer***

- **Palazestrant.** *(Not Yet FDA-Approved for MBC Patients):* **Palazestrant** is a complete estrogen receptor antagonist (CERAN) and a selective ER degrader (SERD) currently being studied for the treatment of ER+, HER2- MBC. **Palazestrant** binds to and inactivates the estrogen receptor whether it is the wild-type (normal) or mutated version. A Phase 1 dose escalation study of this oral drug enrolled 41 heavily pre-treated patients; 95% had previously received at least one prior CDK4/6 inhibitor, 68% had previously taken **fulvestrant (Faslodex)**, and 42% received prior chemotherapy in the advanced setting. Overall, patients received a median of 3 prior lines of anti-cancer therapies. Of 39 patients whose circulating tumor DNA (ctDNA) was assessed, *ESR1* mutations were detected in 49% at baseline. The study found that the clinical benefit rate was 46%. Another Phase 1b/2 trial (NCT05508906) investigating **palazestrant** plus **ribociclib (Kisqali)** or **alpelisib (Piqray)** in patients with ER+, HER2- MBC is ongoing (SABCS 2023 PO4-04-12). Results presented at SABCS 2024 (P2-09-16) showed that the median progression-free survival (PFS) was not reached, 6-month PFS was 72% in all patients, 67% if they had received a prior CDK4/6 inhibitor, 70% if they were *ESR1* wild type, and 81% with an *ESR1* mutation. The clinical benefit rate was 76% in all patients, 71% if patients received a prior CDK4/6 inhibitor, 74% if *ESR1* wild type, and 81% with an *ESR1* mutation. An additional trial is planned. The Phase 3 OPERA-1 trial will test **palazestrant** as monotherapy versus **fulvestrant (Faslodex)** or an aromatase inhibitor in patients with ER+, HER2- MBC who have advanced on 1-2 lines of endocrine therapy (SABCS 2023 PO3-18-09). **From:** ***https://www.globenewswire.com/news-release/2021/11/30/234288***

5/0/en/Olema-Oncology-Announces-First-Clinical-Data-on-OP-1250-in-Advanced-ER-HER2-Breast-Cancer.html

- **Pembrolizumab (Keytruda)**: As reported at SABCS 2023 (PO1-06-02), the single-arm Phase 2 TATEN trial (NCT04251169) evaluated **pembrolizumab (Keytruda)** plus **paclitaxel (Taxol)** in patients with HR+/HER2-, PAM50 non-luminal advanced breast cancer who progressed on CDK4/6 inhibitors. The median progression-free survival (PFS) was 8.3 months. However, 13/18 patients stopped treatment due to progressive disease, and 3 stopped due to toxicity. The trial was halted due to lack of funding and drug supply. Another trial (NCT03051659) showed that addition of **pembrolizumab (Keytruda)** to **eribulin (Halaven)** therapy in patients with HR+ MBC did not provide survival benefits. Data reported at SABCS 2023 (PO1-15-09) suggested that enhancing Vitamin A metabolism in such patients increases the response to **pembrolizumab (Keytruda)**. From: ***https://pubmed.ncbi.nlm.nih.gov/32880602/***
  Currently, **pembrolizumab (Keytruda)** is approved for all cancers–including breast cancers–that have microsatellite instability and those with high tumor mutational burden. Though these findings are rare in ER+ breast cancer, they could affect the treatment.

- **PF-07248144. PF-07248144** is an inhibitor of KAT6A and KAT6B, which are histone lysine acetyltransferases. In a Phase 1, first-in-human trial (NCT04606446), heavily pre-treated patients with ER+, HER2- MBC were treated with **PF-07248144**, either alone or with **fulvestrant (Faslodex).** The median progression-free survival with the combination was 10.7 months. The drug showed a tolerable safety profile. Nothing new was reported for this drug at SABCS 2024. From: ***https://www.practiceupdate.com/c/166494/2/1/?elsca1=emc_enews_daily-digest&elsca2=email&elsca3=practiceupdate_onc&elsca4=oncology&elsca5=newsletter&rid=NTQ3NDQ1MTI3NDI5S0&lid=20844069***
- **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.

- **Samuraciclib (CT-7001)** *(Not Yet FDA-Approved for MBC Patients)*: Samuraciclib is an oral CDK7 inhibitor that showed encouraging results in a Phase 2 study in combination with **fulvestrant (Faslodex)** in patients with advanced HR+, HER2- BC. Thirty-one patients with difficult-to-treat disease were enrolled; 81% had visceral disease, including 45% with liver metastasis. All patients previously progressed following treatment with a CDK4/6 inhibitor. Of the 31 patients, 24 were evaluable for response at the time of data cut-off. Seventeen (71%) had tumor shrinkage, and median progression-free survival (PFS) was 16.1 weeks. Notably, patients with no mutation in the *TP53* gene had a median PFS of 32.0 weeks. Prolonged disease control was also apparent in patients with no liver metastases at baseline, with median PFS having not yet been reached (at the point of this data cut-off, median PFS would be at least 28 weeks). As presented at SABCS 2024 (P2-07-22), the recommended Phase 2 dose was identified (**samuraciclib** 360 mg + **ribociclib (Kisqali)** 400 mg), and preliminary signs of efficacy were found. Only 5 patients were in the recommended dose cohort, and 100% had grade 1/2 diarrhea, 80% had nausea/vomiting, 60% had asthenia (physical weakness, lack of energy and strength). A Phase 2 dose expansion trial is ongoing. **From: *https://www.biospace.com/article/releases/carrick-therapeutics-presents-encouraging-initial-efficacy-for-samuraciclib-ct-7001-in-combination-with-fulvestrant-in-advanced-hr-her2-breast-cancer-patients-at-esmo-congress-2021/***

- **SARMs (Selective Androgen Receptor Modulators)** *(Not Yet FDA-Approved for MBC Patients):* SARMS are a new class of endocrine therapies that function as either androgen receptor (AR) agonists or antagonists. (An agonist is a drug that binds to the receptor and activates it, and an antagonist binds to receptors and stops the receptor from producing a desired response). A percentage of patients with any MBC subtype, including TNBC, have androgen receptor-positive MBC. SARMs such as enobosarm are being studied in clinical trials.

- **SERCAs (Selective Estrogen Receptor Covalent Antagonists)** *(Not Yet FDA-Approved for MBC Patients):* SERCAs are 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 have begun being tested in clinical trials for HR+/HER2- MBC patients who have progressed on prior therapy.
H3B-6545 *(Not Yet FDA-Approved for MBC Patients*): **H3B-6545** is a first-in-class SERCA that targets both wild-type and mutant ER proteins. A Phase 1/2 trial (NCT03250676) of **H3B-6545** was conducted in 151 patients with ER+, HER2- MBC that was refractory to endocrine therapy (ASCO 2024, abstract #1015). Enrolled patients had a median of 2 lines of endocrine-containing therapy (range 1-7 lines) and a median of 1 line of non-endocrine-containing therapy (range 1-6); 90% had received prior CDK4/6 inhibitor therapy). Of 115 patients, 28 (24%) had clonal Y537S *ESR1* mutations. The clinical benefit rate at 6 months—defined as complete response, partial response, or stable disease for at least 23 weeks—was 57.1% in those with a Y537S *ESR1* mutation and 41.5% across all patients. Median progression-free survival (PFS) was 4.6 months in all patients and 7.3 months in those with a Y537S *ESR1* mutation. Median overall survival in all patients was 21.5 months and 18.6 months in those with a Y537S *ESR1* mutation. Responses were observed across patient groups, including those with visceral metastases, *ESR1* mutations, and after prior therapy with CDK4/6 inhibitors, **fulvestrant (Faslodex)**, and chemotherapy. Results suggested greater antitumor activity among patients with *ESR1* Y537S clonal mutations. **From:** ***https://theoncologist.onlinelibrary.wiley.com/doi/full/10.1002/onco.13874?elq_cid=25966017&elq_mid=54046&fbclid=IwAR0yxu7v7q4XN6UUOxunbrA5LhQ-MoN49t6Ao6JF8cJZESsORNh3P8R3QhI&utm_campaign=34397&utm_content=Email-Research-DirectEmal_ONCO_Conf.persp_ASCO_2021-07-02&utm_medium=email&utm_source=eloquaEmail#.YObnzZbqbqc.facebook*** and ***https://ascopubs.org/doi/10.1200/JCO.2024.42.16_suppl.1015***

- **ShERPAs Selective human Estrogen Receptor Partial Agonists** *(Not Yet FDA-Approved for MBC Patients):* ShERPAs represent a new class of drugs that mimics the effects of estradiol in

endocrine-resistant breast cancer cells. A Phase 1 trial (NCT03201913) of a ShERPA called **TTC-352** enrolled 15 patients with ER+ MBC who had progressed on at least two lines of hormone therapy, one of which included a CDK4/6 inhibitor. The median progression-free survival was 58 days. Further development of **TTC-352** is planned. As of 2020, no trials for ShERPAs are open. From: ***https://pubmed.ncbi.nlm.nih.gov/32696319/*** and ***https://ir.lanternpharma.com/news-events/press-releases/detail/112/lantern-pharma-and-ttc-oncology-establish-ai-collaboration***

- **Tamoxifen (Nolvadex) Resistance and Toremifene (Fareston):** For patients whose doctors recommend that they start taking **tamoxifen (Nolvadex),** and for patients who are not responding well to **tamoxifen (Nolvadex),** a "CYP2D6" test may be recommended. This is because some people simply will not respond to **tamoxifen (Nolvadex)** 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 **toremifene (Fareston),** which is a selective estrogen receptor modulator (SERM) similar to **tamoxifen (Nolvadex),** may be a worthwhile choice for postmenopausal (not premenopausal) patients. **From: *https://pmc.ncbi.nlm.nih.gov/articles/PMC10789960/#:~:text=Relevant%20clinical%20trial%20results%2C%20meta,with%20poor%20prognosis%20of%20TAM*.**
- **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 2 weeks, twice, and then once every 4 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. A review published in 2023 indicated that the role of the androgen receptor in MBC may be context dependent, with opposite roles in ER+ versus ER- breast cancer. More work is needed to understand the therapeutic implications of these differences. **From[184, PMID:24596374]:** ***http://www.ncbi.nlm.nih.gov/pubmed/24596374*** and ***https://academic.oup.com/oncolo/article/28/5/383/7087214***

- **Vepdegestrant (ARV-471)** *(Not Yet FDA-Approved for MBC Patients)*: **Vepdegestrant (ARV-471)** is an oral experimental drug (called a PROTAC inhibitor) that degrades estrogen receptors by targeting specific proteins. As reported at SABCS 2023 (PS15-03), it was studied in a Phase 1b dose escalation trial (NCT04072952) that enrolled 46 patients who were heavily pretreated with a median of four prior therapies. Nearly all (87.0%) patients had previously taken CDK4/6 inhibitors, 80.4% had taken **fulvestrant (Faslodex)**, and 76.1% received prior chemotherapy. Of the 47 patients who were evaluable for clinical benefit (confirmed complete response, partial response, or stable disease) the clinical benefit rate was 40%. In the Phase 2 expansion cohort of this trial, median progression-free survival was 3.5 months (SABCS 2023 PO3-05-08). The global, randomized Phase 3 VERITAC-2 study (NCT05654623) will compare efficacy and safety of **vepdegestrant** versus **fulvestrant (Faslodex)** (SABCS 2023 PO1-19-12), and the Phase 3 VERITAC-3 study (NCT05909397) will compare **vepdegestrant** plus **palbociclib (Ibrance)** vs **letrozole (Femara)** plus **palbociclib (Ibrance)** (SABCS 2023 PO2-20-03). Other trials for **vepdegestrant** include NCT05463952, NCT06206837, and NCT06125522. It received FDA fast track designation (i.e., faster review) in February 2024. From:
  https://www.pfizer.com/news/press-release/press-release-detail/arvinas-and-pfizer-announce-protacr-protein-degrader-arv

- **ZN-c5** (*Not Yet FDA-Approved for MBC Patients):* **ZN-c5**, an oral SERD, was studied in a small cohort of 15 HR+, HER2- MBC patients who had received a median of 4 prior lines of therapy. At 6 months, the clinical benefit rate was 40%, with 10 patients exhibiting stable disease and 5 experiencing disease progression. The median progression-free survival was 3.8 months. One trial on **ZN-c5** (NCT04514159) has been completed; no results are available.

Research and Potential Therapies for HER2- (or Low) MBC

Although a patient's HER2 status may be negative as per their pathology report, in some cases HER2-directed treatment may be viable, as is the case with **fam-trastuzumab deruxtecan-nxki (T-DXd; Enhertu)** described below. Furthermore, although the drug **trastuzumab (Herceptin)** is FDA-approved solely for breast cancer patients whose cancer is HER2+, researchers from the University of Michigan report that **trastuzumab (Herceptin)** may help women with HER2- 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 **trastuzumab (Herceptin)**. Surprisingly, the treatment worked for them too. These women were essentially given **trastuzumab (Herceptin)** for a year by mistake! The surprising thing was when the data were analyzed, those women actually benefited more from the **trastuzumab (Herceptin)** than the women whose tumors were HER2+. Their reduction in recurrence was 50%, even though their tumors were classified as HER2-.

The research team hypothesizes that 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- breast cancers may still make HER2, but not in enough quantities to register the cancer as HER2+. But because they are the cells responsible for metastasis, blocking their growth with **trastuzumab (Herceptin)** may lead to fewer recurrences for patients. One researcher theorized 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- breast cancer and showed that HER2+ (not negative) stem cells in these animals spread to the bone, in the same way it does in humans. They also confirmed that **trastuzumab (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-. To their surprise, the researchers located small groups of aggressive, treatment-resistant HER2+ 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+ 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 some patients with HER2- breast cancer may 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- breast cancers. **From[188, PMID:23442322; 189, PMID:PMC3593096]:**
http://healthland.time.com/2013/02/27/herceptin-may-benefit-wider-group-of-breast-cancer-patients/

- **Durvalumab (Imfinzi)** (*Not Yet FDA approved for MBC Patients*)
- **Fam-trastuzumab deruxtecan-nxki (T-DXd; Enhertu)** (*FDA-Approved for HER2+, HER2-Low, and HER2-Ultralow MBC Patients*)
- **Trastuzumab Duocarmazine (SYD985)** (*Not Yet FDA-Approved for MBC Patients*)

- **Durvalumab (Imfinzi)** (*Not Yet Approved for MBC Patients*) **vs. Chemotherapy in Pre-Treated HER2- Patients:** The SAFIR02-IMMUNO Phase 2 trial enrolled HER2- locally advanced and MBC patients (including 82 who had TNBC).

Patients were required to have received prior first- or second-line chemotherapy. Among the 44 patients with PD-L1–positive disease across several MBC subtypes, the median overall survival (OS) was 26 months with the immunotherapy drug **durvalumab (Imfinzi)** compared with 12 months with chemotherapy. For the "mixed" study population of patients with various breast cancer subtypes, median OS was 21.7 months with **durvalumab (Imfinzi)** vs. 17.9 months with chemotherapy. And among the 82 TNBC MBC patients in the trial, the median OS was 21 months on **durvalumab (Imfinzi)** compared with 14 months on chemotherapy. **From:** ***https://www.targetedonc.com/conference/sabcs-2019/durvalumab-maintenance-may-improve-outcomes-in-triplenegative-breast-cancer***

Durvalumab (Imfinzi) in combination with fam-trastuzumab deruxtecan-nxki (T-DXd; Enhertu) was evaluated in the first-line setting in the BEGONIA trial of 46 MBC patients with HR-, HER2-low disease. The median progression-free survival was 12.6 months, and responses were observed irrespective of PD-L1 expression.

- **Fam-trastuzumab deruxtecan-nxki (T-DXd; Enhertu).** *(FDA-Approved for HER2+, HER2-Low, and HER2-Ultralow MBC Patients):* **Fam-trastuzumab deruxtecan-nxki (T-DXd; Enhertu)** was FDA-approved for HER2-low patients based on the results of the Phase 3 DESTINY-Breast04 trial involving patients with HER2-low metastatic breast cancer who had received one or two previous lines of chemotherapy. (Low expression of HER2 was defined as a score of 1+ on immunohistochemical [IHC] analysis or as an IHC score of 2+ and negative results on in situ hybridization). Patients were randomly assigned in a 2:1 ratio to receive **fam-trastuzumab deruxtecan-nxki (T-DXd; Enhertu)** or the physician's choice of chemotherapy. Of the 557 patients who underwent randomization, 494 (88.7%) had hormone receptor–positive disease and 63 (11.3%) had hormone receptor–negative disease (TNBC). In the hormone receptor–positive cohort, the median progression-free survival (PFS) was 10.1 months in the **fam-trastuzumab deruxtecan-nxki (T-DXd; Enhertu)** group and 5.4 months in the chemotherapy group, and overall survival (OS) was 23.9 months vs. 17.5 months. In the TNBC group, the median PFS was 8.5 months in the **fam-trastuzumab deruxtecan-nxki (T-DXd; Enhertu)** group vs 2.9 months in the chemotherapy group, and the median OS was 18.2 months vs 8.3 months. As reported at ASCO 2024 (abstract

#LBA1000), the DESTINY-Breast06 trial (NCT04494425) studied **fam-trastuzumab deruxtecan-nxki (T-DXd; Enhertu)** versus treatment of physician's choice in patients with HER2-low or -ultralow (IHC 0 with membrane staining), HR+ MBC after progression on hormone therapy and no prior chemotherapy in the metastatic setting. Median PFS in the HER2-low group was 13.2 months for **fam-trastuzumab deruxtecan-nxki (T-DXd; Enhertu)** and 8.1 months for physician's choice. In the HER2-ultralow group, median PFS was 13.2 months with **fam-trastuzumab deruxtecan-nxki (T-DXd; Enhertu)** and 8.3 months for physician's choice, showing the same benefit for **fam-trastuzumab deruxtecan-nxki (T-DXd; Enhertu)** in both HER2 groups. As reported at SABCS 2024 (LB1-04), **fam-trastuzumab deruxtecan-nxki (T-DXd; Enhertu)** improved PFS regardless of type of hormone therapy resistance and time to disease progression. As of December 2024, this drug continues to be tested in trials for patients with various HER2 expression levels. **From:** ***https://dailynews.ascopubs.org/do/10.1200/ADN.22.201047/full/*** and ***https://www.cancernetwork.com/view/fam-trastuzumab-deruxtecan-nxki-improves-efficacy-in-metastatic-breast-cancer***

- **Trastuzumab Duocarmazine (SYD985)** *(Not Yet FDA-Approved for MBC Patients):* Duocarmazine is a chemotherapy drug, and linking it with **trastuzumab (Herceptin)** enables the combination drug to find and kill HER2+ cancer cells. The FDA has conferred Fast-Track designation to **trastuzumab duocarmazine** for the treatment of patients diagnosed with HER2+ MBC who had progressed on prior treatment. The FDA has since suspended its decision on approving this drug following the release of a complete response letter requesting more information. As well as being effective in women with high HER2 levels in their tumor, **trastuzumab duocarmazine** was also active in a subset of women with lower levels of the HER2 protein (even as low as IHC 1+/2+, ISH-). Among the 32 patients with HER2-low, HR+ MBC, 9 (28%) achieved an objective (partial) response. And in the group of 15 MBC patients with HER2-low, HR- MBC, 6 (40%) achieved an objective (partial) response. As of December 2024, the Phase 3 TULIP trial (NCT03262935) for this drug is completed with results. **From:** ***https://www.thelancet.com/journals/lanonc/article/PIIS1470-***

2045(19)30328-6/fulltext and *https://www.cancernetwork.com/view/fda-issues-crl-for-trastuzumab-duocarmazine-in-advanced-her2-breast-cancer*

Research and Potential Therapies for HER2+ MBC

- **ARX788** *(Not Yet Approved for MBC Patients)*
- **CDK4/6 Inhibitors** *(FDA-approved for MBC patients)*
- **HER2-Targeted Therapy Plus "Soft" Chemo** *(for older patients)*
- **MCLA-128** *(Not Yet FDA-Approved for MBC Patients)*
- **Niraparib (Zejula) plus trastuzumab (Herceptin)**
- **Palbociclib (Ibrance) and Trastuzumab (Herceptin)**
- **Pembrolizumab (Keytruda)** *(FDA-approved on a limited basis)*
- **Pertuzumab (Perjeta), Trastuzumab (Herceptin), and Gemcitabine (Gemzar)**
- **Pyrotinib** *(Not Yet FDA-Approved for MBC Patients)* **Plus Capecitabine (Xeloda)**
- **Trastuzumab Duocarmazine (SYD985)** *(Not Yet FDA-Approved for MBC Patients)*
- **Trastuzumab (Herceptin), Lapatinib (Tykerb), and Chemotherapy**
- **Trastuzumab (Herceptin) Plus Pertuzumab (Perjeta), with or Without Chemotherapy**
- **Zanidatamab** *(Not Yet FDA-Approved for MBC Patients)*

- **ARX788** *(Not Yet Approved for MBC Patients):* ACE-Breast-03 (NCT04829604) is a Phase 2, multicenter study of **ARX788**, which an anti-HER2 antibody-drug conjugate being evaluated for HER2+ MBC patients whose disease is resistant or refractory to **fam-trastuzumab deruxtecan-nxki (T-DXd; Enhertu), trastuzumab emtansine (T-DM1; Kadcyla),** or **tucatinib (Tukysa)**-containing regimens. As of the data cutoff, seven patients enrolled in the study were previously treated with **trastuzumab emtansine (T-DM1; Kadcyla)** and received a median of five lines of prior anticancer therapies. Five patients were previously treated with HER2 tyrosine kinase inhibitors. The confirmed objective response rate was 57.1% (4 of 7 patients), and the disease control rate was 100%. Patients had a median time on therapy of 7.2 months, and treatment remains ongoing. It is important to bear in mind that although these results are highly encouraging, the reported study population is very small. A Phase 3 trial being conducted in China has shown significant

progression-free survival benefit with **ARX788** compared to control. There are multiple trials that are recruiting and not yet recruiting trials for this compound. NCT06224673 will be for HER2 low. **From:** ***https://aacrjournals.org/cancerres/article/83/5_Supplement/PD18-09/717200/Abstract-PD18-09-ACE-Breast-03-Efficacy-and-safety***

- **CDK4/6 Inhibitors:** Cyclin-dependent kinases are proteins that contribute to the growth and development of cancer cells. **Palbociclib (Ibrance), ribociclib (Kisqali),** and **abemaciclib (Verzenio)** are FDA-approved CDK4/6 inhibitors for HR+, HER2- MBC patients. As of January 2020, there are clinical trials underway to test CDK4/6 inhibitor efficacy (given together with other drugs) on HER2+ MBC patients. The phase 3 PATINA trial (NCT02947685) reported at SABCS 24 (GS2-12) is considered practice changing: for those with triple-positive disease (HER2+ and ER/PR+), a 15-month increase in progression-free survival was observed by adding **palbociclib (Ibrance)** to endocrine therapy and HER2-targeted therapy. From: ***https://sabcs.org/Portals/0/Documents/PATINA_Abstract_12-11-24.pdf?ver=6NaxdWhjPHoc7aD3kzrO4Q%3D%3D*** and ***https://ascopost.com/news/january-2025/addition-of-palbociclib-to-standard-therapy-in-metastatic-hormone-receptor-positive-her2-positive-breast-cancer/***
- **HER2-Targeted Therapy Plus "Soft" Chemo** (for older patients): While **docetaxel (Taxotere)** combined with **trastuzumab (Herceptin)** and **pertuzumab (Perjeta)** have been shown to be effective in younger patients with HER2+ 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 (Herceptin)** and **Pertuzumab (Perjeta)** (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 (Herceptin)** and **pertuzumab (Perjeta)** 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 (Herceptin)** and **pertuzumab (Perjeta)** 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. Dose-reduced

paclitaxel (Abraxane) can also be considered. **From:** ***https://www.medpagetoday.com/hematologyoncology/breastcancer/71076***

- **MCLA-128** *(Not Yet FDA-Approved for MBC Patients):* **MCLA-128 (zenocutuzumab)** 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+ 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 8 months, and seven patients' disease became stable (in four of the seven it was stable more than 5 months). The clinical benefit rate of the treatment was 64%, meaning that 64% of patients either responded to treatment or achieved a stable disease for at least 12 weeks. A trial (NCT02912949) is studying this drug in solid tumors. As reported at ASCO 2020 (abstract #1037), a Phase 2 trial (NCT03321981) enrolling 48 patients with HR+, HER2-low (IHC 1+/IHC 2+ with negative FISH) MBC who had progressed on a CDK4/6 inhibitor and up to 3 lines of hormone therapy and who had received 2 or fewer chemotherapy regimens in the metastatic setting showed that zenocutuzumab provided clinical activity and a favorable safety profile. **From:** ***https://breastcancer-news.com/2017/05/23/initial-trial-results-show-mcla-128-benefits-metastastic-breast-cancer-patients/***
- **Niraparib (Zejula) plus trastuzumab (Herceptin):** The combination of **niraparib (Zejula)**, a PARP inhibitor, plus **trastuzumab (Herceptin)** is being studied in a Phase 1/2 trial for HER2+ MBC, regardless of ER status or *BRCA* status (NCT03368729).

- **Palbociclib (Ibrance) and Trastuzumab (Herceptin)**: 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. 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. 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 **palbociclib (Ibrance)** and **trastuzumab**

(Herceptin) without **letrozole (Femara)** achieved PFS, and 8 of 15 patients who received **palbociclib (Ibrance)** and **trastuzumab (Herceptin)** with **letrozole (Femara)** were also progression free. As reported at ASCO 2024 (abstract #1008), cohort C of the PATRICIA trial (NCT02448420) studied **palbociclib (Ibrance)** plus **trastuzumab (Herceptin)** plus hormone therapy versus physician's choice in patients with HR+, HER2+ MBC who had received at least one HER2-targeted therapy. PFS was significantly longer with **palbociclib (Ibrance)** plus **trastuzumab (Herceptin)** plus hormone therapy (9.1 vs 7.5 months), and 12-month PFS rates were higher for **palbociclib (Ibrance)** plus **trastuzumab (Herceptin)** plus hormone therapy (43.7% and 21.4%). From: ***https://www.onclive.com/conference-coverage/sabcs-2018/palbociclib-combo-active-in-her2-breast-cancer*** and ***https://ascopubs.org/doi/10.1200/JCO.2024.42.16_suppl.1008#:~:text=Palbociclib%20+%20T%20+%20ET%20was%20associated,Clinical%20trial%20information:%20NCT02448420.***

- **Pembrolizumab (Keytruda)**, a PD-1 inhibitor immunotherapy drug: *(FDA-approved for patients with metastatic, microsatellite instability-high [MSI-H], mismatch repair deficient [dMMR], or tumor mutational burden-high (TMB-H) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options)*: For patients with HER2+, PD-L1-positive MBC that is resistant to **trastuzumab (Herceptin)** or **trastuzumab emtansine (T-DM1; Kadcyla)** treatment, the results of the PANACEA clinical trial may be intriguing. The combination of **pembrolizumab (Keytruda)** and **trastuzumab (Herceptin)** reached an objective response rate of 15.2% in patients with **trastuzumab (Herceptin)-** or **trastuzumab emtansine (T-DM1; Kadcyla)-**resistant, PD-L1–positive, HER2+ MBC with an average disease control duration of 11.1 months. Higher levels of stromal tumor-infiltrating lymphocytes (sTILs) were associated with improved response and disease control in the PD-L1-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 PD-L1-negative disease did not respond whatsoever to this treatment. From: ***https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm560040.htm*** and ***https://pubmed.ncbi.nlm.nih.gov/36252998/*** and ***http://www.onclive.com/conference-coverage/sabcs-2017/pembrolizumabtrastuzumab-active-in-her2positive-breast-cancer*** and

- **Pertuzumab (Perjeta), Trastuzumab (Herceptin), and Gemcitabine (Gemzar)**: In a study of 44 HR-, HER2+ MBC patients who had received prior treatment with **pertuzumab (Perjeta)**, a Phase 2 trial found that the triplet combination of **pertuzumab (Perjeta), trastuzumab (Herceptin), and gemcitabine (Gemzar)** provided a median progression-free survival (PFS) of 5.5 months, and the median overall survival rate was still not reached at 27.6 months. One patient had a complete response, 20% experienced a partial response, and disease stabilized in 52% of the group. Notably, 49% of the patients had received prior **trastuzumab emtansine (T-DM1; Kadcyla)**, but the PFS rate at 3 months was similar regardless of whether patients had or had not already been treated with it. **From:** ***https://www.medpagetoday.com/hematologyoncology/breastcancer/83625?xid=nl_mpt_DHE_2019-11-30&eun=g1172363d0r&utm_source=Sailthru&utm_medium=email&utm_campaign=Daily+Headlines+Top+Cat+HeC++2019-11-30&utm_term=NL_Daily_DHE_dual-gmail-definition&fbclid=IwAR3nUw_EZ6GHb2drlFHpMSdfMd7p_u7WGhUe1Jh-R8BbXFM3-2_lXwllKDw*** and ***https://pubmed.ncbi.nlm.nih.gov/31774522/***

- **Pyrotinib** *(Not Yet FDA-Approved for MBC Patients)* **plus Capecitabine (Xeloda): Pyrotinib** is a tyrosine kinase receptor inhibitor that targets HER2, as well as the related proteins HER4 and epidermal growth factor receptor (EGFR), also known as HER1. The PHOEBE trial enrolled 267 Chinese patients with HER2+ MBC who had been previously treated with **trastuzumab (Herceptin)** and up to two previous lines of chemotherapy in the metastatic setting. Patients were randomly assigned to receive either **pyrotinib** plus **capecitabine (Xeloda),** or **lapatinib (Tykerb)** plus **capecitabine (Xeloda)**. The study determined that patients treated with **pyrotinib** plus **capecitabine (Xeloda)** had a 31% lower risk of death than those treated with **lapatinib (Tykerb)** plus **capecitabine (Xeloda),** with overall survival (OS) not reached in the **pyrotinib** arm compared with an OS of 26.9 months in the **lapatinib (Tykerb)** arm. Furthermore, patients in the **pyrotinib** arm had significantly longer progression-free survival (PFS) than those in the **lapatinib (Tykerb)** arm (12.5 months vs 5.6 months), with a 52% lower risk of disease progression. No trial in the US (or anywhere other than China) on **pyrotinib** either as monotherapy or in combination with anything else was found as of December 2024. A real-world study out of China of 239 people, including those with brain mets, was reported in 2024 that showed

a PFS of 8.2-14 months, depending on how many prior lines of therapy (3+ = 8.2 mo PFS, 1st line = 14 mo). In people with brain mets, the PFS was 7.5 months, and median OS was 21.3 months. **From:** ***https://www.aacr.org/about-the-aacr/newsroom/news-releases/investigational-therapy-pyrotinib-with-chemotherapy-may-improve-outcomes-in-patients-with-pretreated-her2-positive-breast-cancer/*** and ***https://pubmed.ncbi.nlm.nih.gov/37589217/***

- **Trastuzumab Duocarmazine (SYD985)** *(Not Yet FDA-Approved for MBC Patients)* The FDA has conferred Fast-Track designation to **trastuzumab duocarmazine** for the treatment of patients diagnosed with HER2+ MBC who had progressed on prior treatment. **Duocarmazine** is a chemotherapy drug, and linking it with **trastuzumab (Herceptin)** enables the combination drug to find and kill HER2+ cancer cells. Among the 48 HER2+ MBC patients in this study, 16 (33%) achieved an objective response (all partial responses). Final results reported at ESMO 2023 (386MO) for the Phase 3 TULIP study (NCT03262935), which enrolled patients with previously treated HER2+ MBC including those with brain metastases, showed that **SYD985** provided a median overall survival of 21.0 months versus 19.5 months for physician's choice of treatment, a difference that was not significant. In May 2023, the FDA issued a complete response letter to the biologics license application submitted by Byondis, the company that makes **SYD985**. The complete response letter requests additional information prior to consideration for approval. **From:** ***https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(19)30328-6/fulltext*** and ***https://www.onclive.com/view/trastuzumab-duocarmazine-provides-numerical-os-benefit-in-pretreated-her2-breast-cancer*** and ***https://www.annalsofoncology.org/article/S0923-7534(23)01399-6/fulltext***

- **Trastuzumab (Herceptin), Lapatinib (Tykerb), and Chemotherapy**: In a study of 285 pre-treated HER2+ MBC patients in China, 88.8% of whom had prior **trastuzumab (Herceptin)** and 49.2% of whom received 2 or more lines of systemic therapy, the combination of **trastuzumab (Herceptin), lapatinib (Tykerb)**, and chemotherapy conferred a median progression-free survival (PFS) of 10.9 months. Patients with brain metastases had a median PFS of 10.2 months. The median

overall survival for all patients has not yet been reached. From: ***https://www.frontiersin.org/articles/10.3389/fonc.2020.00271/full***

- **Trastuzumab (Herceptin) Plus Pertuzumab (Perjeta), with or Without Chemotherapy**: Frontline treatment for HER2+ MBC patients was studied in the Phase 2 PERNETTA trial, which randomized 210 previously untreated HER2+ MBC patients (who were either HR- or HR+) to receive either **trastuzumab (Herceptin)**, **pertuzumab (Perjeta)**, and chemotherapy or **trastuzumab (Herceptin)** and **pertuzumab (Perjeta)** without chemotherapy. Patients whose disease progressed were given **trastuzumab emtansine (T-DM1; Kadcyla)** in the second-line setting. Results announced in July 2019 indicated that the 2-year overall survival (OS) was similar in both groups, although the progression-free survival (PFS) was better in patients taking the chemotherapy combination. For HER2+, HR- patients taking the chemotherapy combination, the median PFS was 22.2 months vs. 8.8 months for the non-chemo group, and the 2-year OS was very close – 79.5% vs. 81.1%. The researchers suggested that frontline **trastuzumab (Herceptin)** and **pertuzumab (Perjeta)** without chemotherapy may be considered for HER2+ patients with low-to-intermediate tumor burden, especially since treatment toxicity is considerably lower without chemotherapy. From: ***https://www.targetedonc.com/publications/targeted-therapy-news/2019/July-2019/patients-with-mbc-have-reduced-toxicity-burden-with-dual-her2targeted-therapy-in-the-front-line*** and ***https://www.annalsofoncology.org/article/S0923-7534(19)48709-7/fulltext#:~:text=2018Open%20Archive-,PERNETTA%3A%20A%20non%2Dcomparative%20randomized%20open%20label%20phase%20II%20trial,UNICANCER%20UC%2D0140%2F1207)***.

  Secondary analysis showed that **trastuzumab (Herceptin)** and **pertuzumab (Perjeta)** without chemotherapy is NOT detrimental to OS. NCCN guidelines do NOT suggest **trastuzumab (Herceptin)** and **pertuzumab (Perjeta)** without chemotherapy for in HER2+ MBC. From: ***https://pubmed.ncbi.nlm.nih.gov/37561451/***

- **Zanidatamab** *(Not Yet FDA-Approved for MBC Patients):* **Zanidatamab** is a bispecific antibody (an artificial protein that can bind to two different types of antigens or two different parts on the same antigen) that is administered intravenously. In a Phase 1 trial of 22 pre-treated HER2+ MBC patients, a median follow-up at 7.1 months determined that **zanidatamab** plus chemotherapy yielded

a confirmed objective response rate (ORR) of 36.4%. Specifically, when paired with zanidatamab, the ORR was 27.3% with **vinorelbine (Navelbine),** 42.9% with **capecitabine (Xeloda),** and 50% with **paclitaxel (Taxol).** Additionally, the combination was associated with a clinical benefit rate of 54.5%, a disease control rate of 86.4%, and a duration of response ranging from 1.6 months to over 22.1 months. The median progression-free survival was 7.3 months. A phase 1/2b trial (NCT05027139) in progress of zanidatamab + evorpacept (CD47 inhibitor) was reported at SABCS24 (PS8-09), with an ORR of 56% and median progression-free survival of 7.4 months in the HER2+ cohort. **From:**
https://www.onclive.com/view/bispecific-antibodies-like-zanidatamab-have-promise-in-heavily-pretreated-her2-breast-cancer

Research and Potential Therapies Solely for TNBC

TNBC MBC patients are encouraged to read the prior section entitled, *"Research and Potential Therapies for HER2- (or Low) MBC"* since the studies therein may be applicable.

- **ABT-888 (Veliparib)** *(Not Yet FDA-Approved for MBC Patients)*
- **Atezolizumab (Tecentriq) in Combination with Other Agents (Provisional FDA approval was withdrawn due to limited efficacy)**
- **Bicalutamide (Casodex)** *(Not Yet FDA-Approved for MBC Patients)*
- **Binimetinib** *(Not Yet FDA-Approved for MBC Patients)*
- **Capivasertib and Taxol** *(FDA-Approved for HR+ MBC Patients)*
- **Datopotamab Deruxtecan** (*Not Yet FDA-Approved for MBC Patients)*
- **Enzalutamide (Xtandi or MDV3100),** an Androgen Receptor Blocking Therapy *(Not Yet FDA-Approved for MBC Patients)*
- **KN046** *(Not Yet FDA-Approved for MBC Patients)*
- **Leronlimab (PRO 140)** *(Not Yet FDA-Approved for MBC Patients)*
- **Melatonin**
- **Neratinib (Nerlynx),** an FDA-approved HER2 Targeted Drug being studied in TNBC
- **Pembrolizumab (Keytruda),** a PD-1 Inhibitor Immunotherapy Drug *(Approved in a Limited MBC Setting)*

- **Rose Hip Extract**
- **SGN-LIV1A (Ladiratuzumab)** *(Not Yet FDA-Approved for MBC Patients)*
- **TAVO (tavokinogene telseplasmid/intratumoral IL-12)** *(Not Yet Approved for MBC Patients)* **plus Keytruda (Pembrolizumab)**
- **Tetrathiomolybdate** (**TM**), a Copper Reduction Drug *(Not Yet FDA-Approved for MBC Patients)*
- **Trilaciclib (Cosela)** *(Not Yet FDA-Approved for MBC Patients)*

- **ABT-888 (Veliparib)** *(Not Yet FDA-Approved for MBC Patients):* This is an oral, potent drug that 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 **paclitaxel (Taxol).** The objective response rate in TNBC was 52%. Among the 21 evaluable TNBC patients, response was 60% in *BRCA1/2*+ patients, 67% in non-*BRCA1/2* patients, and 29% in patients with unknown *BRCA1/2* status. A Phase 2 trial (NCT02595905) enrolled triple-negative germline *BRCA1/2*-mutated, *BRCA*-like (germline *BRCA1/2* wild type but with homologous recombination deficiency), and non-*BRCA*-like MBC patients and studied cisplatin plus **veliparib** or placebo. In the germline *BRCA1/2*-mutated group, median progression-free survival (PFS) was 6.2 months in the **cisplatin** plus **veliparib** group and 6.4 months in the **cisplatin** alone group. In the *BRCA*-like group, median PFS was 5.9 months in the **cisplatin** plus **veliparib** group versus 4.2 months in the **cisplatin** alone group. In the non-*BRCA*-like group, median PFS was 4.0 months in the **cisplatin** plus **veliparib** group versus 3.0 months in the **cisplatin** alone group. Thus, significant improvement was seen in *BRCA*-like but not non-*BRCA*-like patients. A Phase 3 randomized trial (NCT02163694) of **carboplatin** and **paclitaxel (Taxol)** with or without **veliparib** showed that median overall survival (OS) for patients given **veliparib** plus **carboplatin** plus **paclitaxel (Taxol)** was 32.4 months vs 28.2 months for patients given placebo plus **carboplatin** plus **paclitaxel (Taxol)**, a difference that was not significant. The PFS benefit reported earlier did not translate into an OS benefit. A pilot study (NCT02158507) is testing **veliparib**

plus **lapatinib (Tykerb)** in patients with metastatic TNBC. **From[120]:** ***http://abstracts.asco.org/156/AbstView_156_152623.html*** and ***https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(22)00739-2/abstract*** and ***https://pubmed.ncbi.nlm.nih.gov/38309017/***

- **Atezolizumab (Tecentriq)** in combination with **nab-paclitaxel (Abraxane)** had been FDA-approved as initial treatment for TNBC MBC patients with PD-L1-positive tumors, but has now been pulled off the US market (this combination is still available in Europe). **Atezolizumab (Tecentriq)** is being studied in combination with **ipatasertib** and either **paclitaxel (Taxol)** or **nab-paclitaxel (Abraxane)** in a Phase 1b study of 26 TNBC MBC patients who were previously untreated for advanced disease. The triplet combination has demonstrated a confirmed objective response rate of 73%, irrespective of tumor biomarker status such as PD-L1 or *PIK3CA*/*AKT1*/*PTEN* alterations. **From:** ***https://www.roche.com/media/releases/med-cor-2019-04-01.htm***

  Atezolizumab (Tecentriq) is also being studied in combination with **cobimetinib (Cotellic)** and a taxane in previously untreated TNBC MBC patients. In the Colet Phase 2 study, 63 patients with locally advanced or metastatic TNBC were randomized to receive first-line treatment with **atezolizumab (Tecentriq)** + **cobimetinib (Cotellic)** (a MEK kinase inhibitor targeted therapy) paired with either **paclitaxel (Taxol)** or **nab-paclitaxel (Abraxane)**. Among all patients, the response rate was 39% for PD-L1–positive patients and 20% for the PD-L1–negative group. In the **paclitaxel (Taxol)** group, 44% of patients with PD-L1–positive disease responded, whereas only 11% of PD-L1–negative patients responded. In the **nab-paclitaxel (Abraxane)** group, 33% of PD-L1–positive patients responded, whereas 27% of PD-L1–negative patients responded. **From:** ***https://www.targetedonc.com/publications/targeted-therapy-news/2019/tto-nov12019/changes-bring-immunotherapy-to-the-forefront-of-the-breast-cancer-treatment***

  Atezolizumab (Tecentriq) is also being studied in combination with **eganelisib (IPI-549)** and **nab-paclitaxel (Abraxane)**. **Eganelisib** is a targeted therapy that reprograms pro-tumor macrophages to relieve immune suppression and activate anti-tumor T cells. The MARIO-3 trial (NCT03961698, ongoing

as of October 2024) is evaluating the triplet combination of **eganelisib** plus **atezolizumab (Tecentriq)** and **nab-paclitaxel (Abraxane)** in the frontline setting for patients with unresectable locally advanced or metastatic TNBC. Data indicated that 86.8% of patients experienced tumor reduction. Patients with PD-L1–negative (n = 23) and -positive (n = 12) tumors had a disease control rate of 78.2% and 91.7%, respectively. The FDA has granted Fast-Track designation to **eganelisib** in combination with an immune checkpoint inhibitor and chemotherapy for the first-line treatment of TNBC MBC patients. **From:** ***https://www.cancernetwork.com/view/eganelisib-combination-therapies-demonstrate-promising-survival-benefit-in-advanced-urothelial-carcinoma-and-tnbc***

As reported at SABCS 2023 (PS16-02), **atezolizumab (Tecentriq)** plus **bevacizumab (Avastin)** plus **paclitaxel (Taxol)** is being tested in the first-line setting in the single-arm Phase 2 ATRACTIB (NCT04408118) trial. At a median follow-up of 16.7 months, median progression-free survival was 11.0 months, and the estimated 18-month overall survival was 69.4%.

- **Bicalutamide** *(Not Yet FDA-Approved for MBC Patients):* **Bicalutamide (Casodex)** is an anti-androgen 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 ER-, PR-, and androgen receptor positive (AR+) (immunohistochemistry >10%), treatment with **bicalutamide (Casodex)** (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 (PFS) 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 January 2020, there is at least one study of **bicalutamide (Casodex)** for AR+ TNBC MBC patients. As reported at SABCS 2023 (PO3-06-09), a Phase 2 clinical trial (NCT03650894) investigating the combination of **nivolumab (Opdivo), ipilimumab (Yervoy),** and **bicalutamide (Casodex)** in triple-negative, AR+ patients showed that progression-free survival was 119 days, and overall survival was 506 days. **Bicalutamide (Casodex)** continues to be tested in combination with **abemaciclib (Verzenio**; NCT05095207, NCT06365788) and in combination with **ribociclib (Kisqali**; NCT03090165). **From:**

http://www.ascopost.com/issues/june-10-2017/targeting-the-androgen-receptor-in-breast-cancer/

- **Binimetinib** *(Not Yet FDA-Approved for MBC Patients):* Binimetinib is an oral MEK inhibitor being studied in combination with **pembrolizumab (Keytruda)** in TNBC MBC patients. A Phase 1/2 study evaluated 17 patients who had ≤3 prior lines of therapy. Objective responses were observed in 29.4% of patients, with 1 complete response (CR) and 4 partial responses (PR). The clinical benefit rate was 35.29% with 6 out of 17 having had CR, PR, or stable disease ≥24 weeks. However, all 5 patients with liver metastases did not respond. **From**: ***https://aacrjournals.org/cancerres/article/83/5_Supplement/P4-01-17/718164/Abstract-P4-01-17-Phase-I-II-study-of***. As reported at SABCS 2023 (PS12-07), a Phase 2 trial (NCT04494958) enrolling patients with metastatic TNBC and 1-2 prior lines of therapy tested **binimetinib** and **palbociclib (Ibrance)** and showed a median progression-free survival of 1.83 months; the trial did not meet its primary endpoint. **Binimetinib** continues to be tested with or without **fulvestrant (Faslodex)** in a Phase 2 trial (NCT05554354) in people with MBC with an *NF1* mutation. A Phase 2 trial (NCT03971409) is testing **binimetinib** in combination with **avelumab (Bavencio)**.

- **Capivasertib (Truqap) and Paclitaxel (Taxol)***:* The Phase 2 PAKT trial enrolled 140 TNBC MBC patients who had not received prior therapy for their metastatic disease, although the majority had taken adjuvant therapy for their earlier stage breast cancer. Patients were randomly assigned to either **paclitaxel (Taxol)** alone, or to **paclitaxel (Taxol)** plus the AKT inhibitor **capivasertib (Truqap)**. Most of the patients (69%) had visceral involvement, and 46% had metastases in three or more organs. Although the median progression-free survival (PFS) difference was minimal at 5.9 months in the **capivasertib (Truqap)** + **paclitaxel (Taxol)** group vs. 4.2 months in the **paclitaxel (Taxol)**-only group, the median overall survival difference was notable at 19.1 months in the **capivasertib (Truqap)** + **paclitaxel (Taxol)** group compared with 12.6 months in the **paclitaxel (Taxol)**-only group. Among the subgroup of 28 patients with *PIK3CA*/*AKT1*/*PTEN*-altered tumors, the median PFS was 9.3 months for patients taking **capivasertib (Truqap)** + **paclitaxel (Taxol)** vs. 3.7 months in the **paclitaxel (Taxol)**-only group. A Phase 2 trial (NCT03801369) testing the combination of

capivasertib (Truqap) and **olaparib (Lynparza)** is recruiting. **From:** ***https://www.healio.com/hematology-oncology/breast-cancer/news/online/%7B66119309-4ade-411c-a6e9-521c510a258a%7D/capivasertib-plus-paclitaxel-improves-survival-in-triple-negative-breast-cancer***

- **Datopotamab Deruxtecan (Dato-DXd; Datroway)**: **Datopotamab Deruxtecan (Dato-DXd; Datroway)** is FDA approved for HR+, HER2- MBC, and continues to be tested in triple-negative MBC (NCT06176261, NCT06103864). This drug is an antibody-drug conjugate (ADC) that was studied in the TROPION-PanTumor01 Phase 1 Trial. The 44 patients enrolled in the study had been treated with a median of three prior therapies in the metastatic setting, including taxanes, platinum-based chemotherapy, immunotherapy, other ADCs, and PARP inhibitors. The overall objective response rate (ORR) was 34%, and in the subgroup of 27 patients who had not previously been treated with a TROP-2-directed drug (such as **sacituzumab govitecan-hziy (Trodelvy))** the ORR was 52%. **From:** ***https://pharmaphorum.com/news/az-daiichi-take-aim-at-gilead-in-triple-negative-breast-cancer/***
  The Phase 1b/2 BEGONIA study (NCT03742102) evaluated the immune checkpoint inhibitor **durvalumab in combination with the TROP2 ADC datopotamab deruxtecan (Dato-DXd).** Preliminary results of the basket BEGONIA trial showed that the combination has strong activity as first-line treatment in advanced or metastatic triple-negative breast cancer among patients with no specific biomarkers for study inclusion. As reported at ESMO 2023 (379MO), median progression-free survival (PFS) was 13.8 months. **Datopotamab deruxtecan (Dato-DXd; Datroway)** has also been studied as monotherapy in the Phase 1 TROPION-PanTumor01 (NCT03401385) trial; PFS was 4.4 months in patients with metastatic TNBC. **From:** ***https://ascopost.com/issues/october-10-2022-supplement-breast-cancer-almanac/begonia-trial-reports-activity-with-datopotamab-deruxtecan-plus-durvalumab-in-triple-negative-breast-cancer/*** and ***https://ascopubs.org/doi/10.1200/JCO.23.01909***

- **Enzalutamide (Xtandi or MDV3100), an Androgen Receptor (AR) Blocker** *(Not Yet FDA-Approved for MBC Patients):* Just as a large number of breast cancers are ER positive, a majority of

breast cancers are 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[150, PMID:24451109]**

In a Phase 2 trial, **enzalutamide (Xtandi)** was tested in 118 patients with AR+ advanced TNBC patients with any number of prior treatments whose AR positivity was any expression (>0%) by immunohistochemistry, and this definition was applied to the intent-to-treat population. An additional 75 patients had AR levels ≥10%, and this definition was applied to the evaluable population.

In the intent-to-treat population of 118 patients, the clinical benefit rates (CBR) were 25% at 16 weeks (the primary endpoint) and 20% at 24 weeks. In the evaluable population of 75 patients, the CBRs were 35% at 16 weeks and 29% at 24 weeks, respectively. Median progression-free survival (PFS) 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 PFS. 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.

A Phase 2 trial (NCT02953860) that tested **enzalutamide (Xtandi)** plus **fulvestrant (Faslodex)** in 28 women with ER-positive, HER2-negative MBC showed that the CBR at 24 weeks was 25%, and median PFS was 8 weeks. From: ***https://www.nature.com/articles/s41523-023-00544-z***

Results for a Phase 2 trial (NCT02091960) testing **enzalutamide (Xtandi)** plus **trastuzumab (Herceptin)** in HER2-positive, AR+ MBC showed that the CBR at 24 months was 24% but 4/103 people had fatal treatment-emergent adverse effects. From: ***https://pmc.ncbi.nlm.nih.gov/articles/PMC8062601/#:~:text=Conclusions,to%20benefit%20from%20this%20combination.***

A Phase 2 trial (NCT06099769) is testing **enzalutamide (Xtandi)** with or without **mifepristone (Mifeprex)** in AR+ metastatic TNBC or ER-low MBC.

(Note: A less promising androgen drug is **abiraterone acetate (Zytiga)**, which was studied in a small group of triple-negative patients (38% with AR expression ≥10%). It resulted in a 24-week CBR of 20% at 24 weeks with a median PFS of less than 3 months)**.** **From:** ***http://www.ascopost.com/issues/june-10-2017/targeting-the-androgen-receptor-in-breast-cancer/***

- **KN046** *(Not Yet FDA-Approved for MBC Patients):* **KN046** is a CTLA-4 blocker that functions as an immune checkpoint inhibitor and downregulates immune responses. A Phase 2 study enrolled 27 TNBC MBC patients who had not received prior therapy for their MBC. Participants were treated with **KN046** and **nab-paclitaxel (Abraxane)**. The confirmed objective response rate was 33.3%, the disease control rate was 88.9%, and clinical benefit rate was 48.1%. Duration of response was 11.9 months, and the median progression-free survival was 7.3 months. Both PD-L1-positive and -negative patients derived overall survial (OS) benefit from the combination treatment, with a 2-year OS rate of 57.14% and 62.5%, respectively. **From SABCS 2022 Poster Spotlight Discussion 11: Improving Outcome for TNBC: New Directions in Immunotherapy**
  As of December 2024, no US trials are being conducted for KN046.

- **Leronlimab (PRO 140)** *(Not yet FDA-approved for MBC patients):* **Leronlimab** is a monoclonal antibody administered subcutaneously with chemotherapy that has shown encouraging results among metastatic TNBC patients whose cancer was confirmed to be CCR5-positive by immunohistochemistry testing. Investigators reported that the 30 patients who received **leronlimab** experienced a 400% to 660% increase in mean progression-free survival and a 570% to 980% increase in 12-month median overall survival. Additionally, a 73% decrease in circulating tumor cells was observed in this patient population. In 2022, a compassionate use study of leronlimab was discontinued (NCT04313075). **From:** ***https://www.cancernetwork.com/view/leronlimab-provides-a-significant-survival-benefit-in-metastatic-triple-negative-breast-cancer***

- **Melatonin as a Possibility for TNBC:** An early-stage study showed 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[195, PMID:24416386]:** ***http://www.scienceworldreport.com/articles/12478/20140128/melatonin-slow-tumor-growths-breast-cancer.htm***

- **Nab-paclitaxel (Abraxane) 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 (Abraxane)/carboplatin** doublet arm had a median progression-free survival (PFS) of 7.4 months versus 5.4 months with **nab-paclitaxel (Abraxane)/gemcitabine (Gemzar)**, and 6.0 months with **gemcitabine (Gemzar)/carboplatin**. Moreover, the 12-month PFS rates were 27%, 13%, and 11%, respectively; hence the 12-month PFS for **nab-paclitaxel (Abraxane) and carboplatin** was more than double the other combination regimens**. From:** ***http://www.onclive.com/web-exclusives/yardley-discusses-evolving-role-of-nabpaclitaxel-in-tnbc***

- **Neratinib (Nerlynx): Neratinib (Nerlynx)** was FDA-approved in Feb. 2020 for a subset of HER2+ MBC patients. NCCN recommends consideration of **neratinib (Nerlynx)** for patients with HER2-negative metastatic breast cancer, regardless of estrogen receptor (ER) status, with activating mutations in the *HER2* gene as detected by next-generation sequencing of tumor tissue or circulating tumor DNA. Also, **neratinib (Nerlynx)** plus **capecitabine (Xeloda)** is in the NCCN guidelines for 4th line therapy and above.
  As reported at ASCO 2024 (abstract #1094), a cohort of patients in SUMMIT (NCT01953926) with HER2-mutant, triple-negative MBC received **neratinib (Nerlynx)** alone or **neratinib (Nerlynx)** plus **trastuzumab (Herceptin)**. Progression-free survival was 2.9 months in the **neratinib (Nerlynx)**-only group and 6.2 months in

the combination group. A Phase 1 trial (NCT06008275) is testing **neratinib (Nerlynx)** plus **ruxolitinib (Jakafi)** in triple-negative MBC.

- **Pembrolizumab (Keytruda, a PD-1 Inhibitor Immunotherapy Drug** *(Approved in a Limited MBC Setting).* **Pembrolizumab (Keytruda)** is 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. **Pembrolizumab (Keytruda)** has already been FDA-approved for any cancer patient who has metastatic, microsatellite instability-high (MSI-H), mismatch repair deficient (dMMR), or tumor mutational burden-high (TMB-H) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options. **Pembrolizumab (Keytruda)** in combination with chemotherapy was FDA-approved in Nov. 2020 for TNBC MBC patients with PD-L1-positive tumors.
  Based upon recent research, **pembrolizumab (Keytruda)** was effective in MBC patients with TNBC, according to an international clinical trial led by NYU. The trial investigated **pembrolizumab (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, **pembrolizumab (Keytruda)** shrank 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 **pembrolizumab (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, PD-L1 expression did not impact patients' outcomes for MBC patients with TNBC who took **pembrolizumab (Keytruda)**. **From:** ***https://www.eurekalert.org/pub_releases/2017-06/nlmc-ide060117.php***

  Recent study results indicate that **pembrolizumab (Keytruda)** may be effective when administered with other drugs. According to the IMPRIME1 Phase 2 study, **pembrolizumab (Keytruda)** combined with a novel immune activator called "Imprime PGG"

demonstrated promising clinical activity as second-line or later treatment for TNBC MBC patients (including those with visceral disease). Imprime PGG activates the immune system to reprogram the immunosuppressive tumor microenvironment and stimulate antigen-specific T cells. The trial included 44 patients, a third of whom had received 3 or more prior lines of therapy. Of the participants, 38.6% of patients achieved stable disease, and 25% had their disease controlled (complete response, partial response or stable disease) for at least 24 weeks. The median progression-free survival (PFS) was 2.7 months, and the median overall survival (OS) was 16.4 months. More than half (57.6%) of patients survived for 12 months, and 36.7% survived at least 18 months. Researchers observed a particularly pronounced clinical benefit in a subgroup of patients who initially were diagnosed with ER-positive/PR-positive disease but progressed on endocrine therapy and - prior to treatment in the study - had biopsies that confirmed conversion to TNBC MBC. These patients had all received prior treatment with **tamoxifen (Nolvadex)**, aromatase inhibitors, or CDK4/6 inhibitors, and all had received at least one line of chemotherapy after development of metastatic disease. In this group, six (50%) achieved response to the combination, four (33%) achieved stable disease and six (50%) achieved disease control for 6 months. The median OS in this group was 17.1 months. **From:** ***https://www.healio.com/hematology-oncology/breast-cancer/news/online/%7Bf27d97f1-33cc-471c-b899-0ae72ad68d03%7D/novel-immuno-oncology-combination-demonstrates-activity-in-metastatic-triple-negative-breast-cancer?page=2***

As presented at SABCS 2023 (GS01-05), the Phase 2 KEYLYNK-009 trial (NCT04191135) enrolled 271 patients with locally recurrent or metastatic TNBC to compare **pembrolizumab (Keytruda)** plus chemotherapy with **pembrolizumab (Keytruda)** plus **olaparib (Lynparza)**. No significant difference in PFS was seen between the two arms in the overall population. However, among patients with a *BRCA* mutation, longer PFS and OS were found. PFS was 12.4 months in the **pembrolizumab (Keytruda)** plus **olaparib (Lynparza)** group and 8.4 months in the **pembrolizumab (Keytruda)** plus chemotherapy group, a difference that was numerically higher but not significantly different. Similarly, OS was not reached and 23.4 months, a numerically higher difference. From: ***Pembrolizumab plus olaparib does not extend survival in triple-negative breast cancer***

Not all patients respond to immune checkpoint inhibitors such as **pembrolizumab (Keytruda)**. A scoring system called LORIS was developed that predicts which patients will respond. From: ***https://www.practiceupdate.com/c/166680/2/1/?elsca1=emc_enews_daily-digest&elsca2=email&elsca3=practiceupdate_onc&elsca4=oncology&elsca5=newsletter&rid=NTQ3NDQ1MTI3NDI5S0&lid=20844069*** As of December 2024, **pembrolizumab (Keytruda)** continues to be studied in combination with other treatments for metastatic TNBC in numerous clinical trials.

- **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%. 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). As of December 2024, no trials are testing rose hip extract. **From:** ***http://www.sciencedaily.com/releases/2015/03/150329141007.htm***

- **SGN-LIV1A (Ladiratuzumab vedotin):** *(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, defined as patients achieving a complete response (CR), PR, or stable disease (SD), was 67% and the clinical benefit rate, 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

December 2024, NCT03310957 is completed, and enrollment in arms testing SGN–LIV1A in NCT03424005 is closed. **From:** ***https://adcreview.com/news/sgn-liv1a-monotherapy-data-show-37-orr-heavily-pretreated-triple-negative-metastatic-breast-cancer/***

- **TAVO (tavokinogene telseplasmid/intratumoral IL-12) plus pembrolizumab (Keytruda):** The KEYNOTE-890 Phase 2 trial (NCT03567720) provided the combination of TAVO and the PD-L1 immunotherapy drug **pembrolizumab (Keytruda)** to metastatic TNBC patients who were refractory to chemotherapy and had progressed after an average of three prior lines of therapy. IL-12 is an immunotherapy that plays a significant role in priming and maintaining T-helper cells, activating natural killer cells, and regulating the reactivation and survival of memory T cells. Four (28.6%) of the evaluable 14 patients showed a rapid tumor reduction and had a confirmed partial response (including a deep partial response in a patient with multiple liver, bone, skin, and nodal metastases and a short disease-free interval following neoadjuvant chemotherapy). All responses are ongoing (range 6 to 9 months), and the median duration of response has not yet been reached. Notably, 3 of the 4 responding patients' lesions were PD-L1 negative. An additional three (21.4%) of the 14 patients had stable disease. As of December 2024, this trial is active but not recruiting. **From:** ***https://www.biospace.com/article/oncosec-presents-interim-data-of-28-5-percent-objective-response-rate-from-ongoing-keynote-890-study-evaluating-tavo-in-combination-with-keytruda-for-heavily-pretreated-late-stage-metastatic-triple-negative-breast-cancer-a***

- **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 followed 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[164, PMID:10656425]: *http://clincancerres.aacrjournals.org/content/6/1/1.full***

- **Trilaciclib (Cosela)** (*(Not Yet FDA-Approved for MBC Patients):* **Trilaciclib (Cosela)** is a newly studied intravenous CDK4/6 inhibitor. In a randomized Phase 2 clinical trial of 102 TNBC MBC patients who had received up to two prior chemotherapy regimens, patients who received **trilaciclib (Cosela)** with **gemcitabine (Gemzar)/carboplatin** chemotherapy had median overall survival (OS) values of 17.8 to 20.1 months compared to 12.6 months for patients on **gemcitabine** (**Gemzar)/carboplatin** chemotherapy alone. As reported at SABCS 2023 (PO2-06-12), a Phase 2 trial (NCT02978716) showed that patients with metastatic TNBC who received **trilaciclib (Cosela)** followed by subsequent cytotoxic chemotherapy had longer survival than those who had not previously received **trilaciclib (Cosela)** (OS 32.7 months versus 12.8 months). As reported at ASCO 2024 (abstract #1091), data from a Phase 2 trial (NCT05113966) showed that the use of **trilaciclib (Cosela)** prior to **sacituzumab govitecan-hziy (Trodelvy)** provided a median progression-free survival of 4.1 months and OS of 15.9 months. Adverse events included neutropenia (40%), anemia (10%), and diarrhea (43.3%). However, data from the phase 3 PRESERVE 2 trial (NCT04799249) in which patients with metastatic TNBC received **trilaciclib (Cosela)** prior to **gemcitabine (Gemzar)** and carboplatin or placebo plus

gemcitabine (Gemzar) and carboplatin showed no OS benefit from the addition of **trilaciclib (Cosela)**. **From:** ***http://investor.g1therapeutics.com/news-releases/news-release-details/g1-therapeutics-presents-updated-data-esmo-2019-randomized-phase*** and ***Trilaciclib Before Gemcitabine/Carboplatin Misses OS End Point in Metastatic TNBC***

Research and Potential Therapies for Hormone Receptor-Positive, HER2+ MBC

Patients with hormone receptor-positive, HER2+ ("Triple Positive") MBC are encouraged to read the sections entitled, "*Research and Potential Therapies for Hormone Receptor-Positive MBC*" and "*Research and Potential Therapies for HER2+ MBC*" because some studies therein may be applicable to Triple-Positive patients.

- **Abemaciclib (Verzenio), Trastuzumab (Herceptin), and Fulvestrant (Faslodex)**
- **Aromatase Inhibitor, Trastuzumab (Herceptin), and Pertuzumab (Perjeta)**
- **Aromatase Inhibitor, Trastuzumab (Herceptin), and Lapatinib (Tykerb)**
- **Palbociclib (Ibrance) and Trastuzumab (Herceptin), with or without Letrozole (Femara)**
- **Palbociclib (Ibrance), Trastuzumab (Herceptin), and hormone therapy**
- **Palbociclib (Ibrance) and Tucatinib (Tukysa) with Letrozole (Femara)**
- **Trastuzumab (Herceptin) and Pertuzumab (Perjeta), with or Without Chemotherapy**
- **Zanidatimab**

- **Abemaciclib (Verzenio), Trastuzumab (Herceptin), and Faslodex (Fulvestrant).** The Phase 2 "MonarcHER" trial determined that the "triplet" combination of **abemaciclib (Verzenio), trastuzumab (Herceptin)**, and **fulvestrant (Faslodex)** showed a significant statistical improvement in progression-free survival (PFS) compared with chemotherapy and **trastuzumab (Herceptin)** in MBC patients with HR+, HER2+ breast cancer. The 225 patients in the study had a median of 4

prior lines of therapy, and were randomized into 3 arms: **abemaciclib (Verzenio)/trastuzumab (Herceptin)/fulvestrant (Faslodex)** (Arm A)**, abemaciclib (Verzenio)/trastuzumab (Herceptin)** (Arm B), or **trastuzumab (Herceptin)** plus physician's choice of chemotherapy (Arm C). The study revealed that the median PFS was longer in Arm A at 8.3 months versus 5.7 months in arms B and C. A secondary endpoint, objective response rate, was also highest in arm A (35%) compared with arms B (16.5%) and C (22.8%). These data suggest that synergy exists among endocrine therapy, CDK4/6 inhibition, and anti-HER2 therapy, and the investigators are considering a Phase 3 confirmatory study of the triplet combination. Final results at ESMO 2022 suggest that a triple-agent, chemotherapy-free treatment regimen may improve overall survival in patients with HR+, HER2+ advanced breast cancer, although NCCN guidelines do not yet recommend this. **From:** ***https://www.targetedonc.com/news/abemaciclib-triplet-prolongs-pfs-in-hrher2-breast-cancer-***

- **Aromatase Inhibitor + Trastuzumab (Herceptin) + Pertuzumab (Perjeta):** The Phase 2 PERTAIN study enrolled 258 women with HER2+, HR+ locally advanced or MBC who were not previously treated with systemic non-hormonal therapy in the advanced-disease setting. Patients received either **trastuzumab (Herceptin)** (with or without a taxane for 18–24 weeks) plus an aromatase inhibitor **(anastrozole (Arimidex)** or **letrozole (Femara)),** or else they received **trastuzumab (Herceptin)** (with or without a taxane for 18–24 weeks) plus **pertuzumab (Perjeta)** plus an aromatase inhibitor. The triplet combination of **trastuzumab (Herceptin)** (with or without a taxane), plus **pertuzumab (Perjeta)** and an aromatase inhibitor resulted in a median progression-free survival of 18.9 months compared to 15.8 months for **trastuzumab (Herceptin)** (with or without a taxane) plus an aromatase inhibitor. Furthermore, the duration of response 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, Trastuzumab (Herceptin), 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 **trastuzumab (Herceptin)** plus chemotherapy in similar settings. The median progression-free survival (PFS) was 11 months for the triplet therapy combination versus 5.7 months for women assigned to **trastuzumab (Herceptin)** plus AI, and the median PFS also favored the triplet compared to **trastuzumab (Herceptin)** plus AI (8.3 months vs 5.7 months). Although overall survival (OS) data were immature at the time of this analysis, they trended in favor of the triplet therapy versus **trastuzumab (Herceptin)** plus AI (median OS, 46.0 vs 40.0 months). The researchers concluded that the PFS benefit obtained with **lapatinib (Tykerb)** plus **trastuzumab (Herceptin)** plus AI in patients with HER2+, HR+ 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:**
http://www.onclive.com/web-exclusives/dual-her2-blockade-superior-for-pfs-in-her2hr-metastatic-breast-cancer

- **Palbociclib (Ibrance) and Trastuzumab (Herceptin), with or without Letrozole (Femara):** 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 HR+. 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 **palbociclib (Ibrance)** + **trastuzumab (Herceptin)** with or without **letrozole (Femara)**. 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 **palbociclib (Ibrance)** and **trastuzumab (Herceptin)** without letrozole **(Femara)** achieved

progression-free survival (PFS), and 8 (53%) of 15 ER+/HER2+ MBC patients who received **palbociclib (Ibrance)** and **trastuzumab (Herceptin)** with **letrozole (Femara)** were also progression-free. (5 (33%) of 15 the patients in the ER-/HER2+ cohort attained PFS at 6 months with **palbociclib (Ibrance)** and **trastuzumab (Herceptin)**). **From:** ***https://www.onclive.com/conference-coverage/sabcs-2018/palbociclib-combo-active-in-her2-breast-cancer***

- **Palbociclib (Ibrance), Trastuzumab (Herceptin), and hormone therapy:** The Phase 3 PATINA trial (NCT02947685) tested addition of **palbociclib (Ibrance)** to HER2-directed therapy plus hormone therapy in the first-line setting in patients with HR+, HER2+ MBC. Patients first received induction therapy with chemotherapy plus **trastuzumab (Herceptin)** with or without **pertuzumab (Perjeta)**. Those who did not progress were randomized to anti-HER2 therapy and endocrine therapy with or without **palbociclib (Ibrance)**. Median progression-free survival was 44.3 months with **palbociclib (Ibrance)** and 29.1 months without (SABCS 2024, GS2-12). From: ***https://www.news-medical.net/news/20241212/PATINA-trial-demonstrates-benefit-of-palbociclib-in-HR2b-HER22b-metastatic-breast-cancer.aspx***
- **Palbociclib (Ibrance) and Tucatinib (Tukysa) with Letrozole (Femara): Palbociclib (Ibrance)** in combination with endocrine therapy has been approved for HR+, HER2- MBC patients, and the combination of **tucatinib (Tukysa)** with **capecitabine (Xeloda)** and **trastuzumab (Herceptin)** (or **trastuzumab and hyaluronidase-oysk (Herceptin Hylecta)** or an approved biosimilar) has been approved for HER2+ MBC patients who have received one or more HER2-directed therapies in the metastatic setting. A Phase 1b/2 study enrolled 42 pre-treated HR+, HER2+ MBC patients, including those with stable central nervous system (CNS) metastasis. Among the 40 evaluable patients, the median progression-free survival was 8.9 months, and the clinical benefit rate was 71%. Notably, patients with CNS metastasis fared just as well as those without. The study determined that a reduced dosage of **palbociclib (Ibrance)** of 75 mg daily was just as effective in the combination as the standard (125 mg) dose.
- **Trastuzumab (Herceptin) and Pertuzumab (Perjeta), with or Without Chemotherapy:** Frontline treatment for HER2+ MBC

patients was researched in the Phase 2 PERNETTA trial, which randomized 210 previously untreated HER2+ MBC patients (some of whom were triple positive) to receive either **trastuzumab (Herceptin)**, **pertuzumab (Perjeta)**, and chemotherapy vs. **trastuzumab (Herceptin)** and **pertuzumab (Perjeta)** without chemotherapy. Patients whose disease progressed were given **trastuzumab emtansine (T-DM1; Kadcyla)** in the second-line setting. Results announced in July 2019 indicated that the 2-year overall survival (OS) was similar in both groups, although the progression-free survival (PFS) was better in Group 1. For HER2+, HR+ patients taking **trastuzumab (Herceptin), pertuzumab (Perjeta),** plus chemotherapy, the median PFS was 23.7 months vs. 8.3 months for patients on the non-chemotherapy regimen, and the OS was very close – 74.2% vs. 75%. The researchers suggested that frontline **trastuzumab (Herceptin)** and **pertuzumab (Perjeta)** without chemotherapy (but with endocrine therapy) may be considered for triple-positive patients with low-to-intermediate tumor burden, especially since treatment toxicity is considerably less without chemotherapy. **From:** ***https://www.targetedonc.com/publications/targeted-therapy-news/2019/July-2019/patients-with-mbc-have-reduced-toxicity-burden-with-dual-her2targeted-therapy-in-the-front-line***

- **Zanidatamab** *(Not Yet FDA-Approved for MBC Patients)*: **Zanidatamab** is a bispecific antibody (an artificial protein that can bind to two different types of antigens or two different parts on the same antigen) that is administered intravenously. As presented at SABCS 2023 (LBO1-04), a Phase 2a trial (NCT04224272) of 51 heavily pre-treated HER2+, HR+ MBC patients, including 18% with brain metastases, with a median follow-up of 16 months determined that **zanidatamab** plus **palbociclib (Ibrance)** plus **fulvestrant (Faslodex)** yielded a median progression-free survival of 12 months. From: Best of SABCS® | Highlights 6030

Research and Potential Therapies 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.

PARP is an enzyme that 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 and European Approved Therapies for *BRCA*- Positive HER2- MBC Patients:

- **Olaparib (Lynparza)** ***(FDA-Approved as a monotherapy) and also approved in Europe***
- **Talazoparib (Talzenna)** ***(FDA-approved as a monotherapy and also approved in Europe)***

- **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- 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- MBC patients with germline *BRCA* mutations who had received no more than 2 prior chemotherapy regimens in which **olaparib (Lynparza)** was compared with a single-agent therapy of the physician's choice. Median progression-free survival (PFS) was significantly longer in the **olaparib (Lynparza)** group than in the standard therapy group (7.0 months vs. 4.2 months), and the response rate was 59.9% in the **olaparib (Lynparza)** group and 28.8% in the standard-therapy group. The overall survival (OS) was 2.2 months longer for **olaparib (Lynparza)** (19.3 months with **olaparib (Lynparza)** vs 17.1 months with standard chemotherapy). Significantly, **olaparib (Lynparza)** is better tolerated than chemotherapy. **From:** ***https://www.medscape.com/viewarticle/895337***

- **Talazoparib (Talzenna)***:* **Talazoparib (Talzenna)** 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-. 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 (Talzenna)**. Patients must be selected for **talazoparib (Talzenna)** based on this FDA-approved companion diagnostic.

  In terms of the potency of PARP inhibition, **talazoparib (Talzenna)** surpasses **veliparib**, **olaparib (Lynparza)**, **rucaparib (Rubraca)**, and **niraparib (Zejula)**.

  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 (Talzenna)** compared to patients who received physician's choice standard of care chemotherapy. The median PFS was 8.6 months for patients treated with **talazoparib (Talzenna)** 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 (Talzenna)** group was more than twice that of the control arm (62.6% for the **talazoparib (Talzenna)** group vs. 27.2% for the chemotherapy group). The study concluded that **talazoparib (Talzenna)** demonstrated superior clinical benefit in all subsets of patients, regardless of receptor subtype (HR+ or TNBC), 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- MBC Patients:

- **Carboplatin vs. Docetaxel (Taxotere)**
- **Lurbinectedin (PM01183)** *(Not Yet FDA-Approved for MBC Patients)*

- **Olaparib (Lynparza) and Durvalumab (Imfinzi)** *(Combination Not Yet FDA-Approved for MBC Patients)*
- **Olaparib (Lynparza), fulvestrant (Faslodex), and palbociclib (Ibrance)**
- **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 (Taxotere)**. 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 (Taxotere)** group vs. 4.6 months for *BRCA1/2* mutation-negative **docetaxel (Taxotere)** group. **From: *https://pmc.ncbi.nlm.nih.gov/articles/PMC4363856/pdf/IJMPO-36-66.pdf***
- **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/m^2 dose, and 44% in patients dosed at 3.5 mg/m^2, 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%. Greater benefit was seen in patients with *BRCA1/2* mutation (progression-free survival (PFS) 4.6 months; overall survival (OS) 20.0 months) vs those without or whose mutation status was unknown (PFS 2.5 months; OS 12.5 months). This drug continues to be tested in patients with solid tumors. **From[196]: *http://www.esmo.org/Conferences/Past-Conferences/ESMO-2016-Congress/News-Articles/Antitumour-Activity-Demonstrated-Wit***

h-Lurbinectedin-in-Patients-With-Metastatic-Breast-Cancer-and-BRCA-Mutations and ***https://ascopubs.org/doi/10.1200/JCO.2018.78.6558***

- **Olaparib (Lynparza) in combination with Durvalumab (Imfinzi)** *(Combination Not Yet FDA-Approved for MBC Patients):* **Durvalumab (Imfinzi)** is a PD-L1 inhibitor being studied in HER2- MBC patients with *BRCA1* or *BRCA2* germline mutations. MEDIOLA was a Phase 1/2 study evaluating the combination of **olaparib (Lynparza)**, an FDA-approved PARP inhibitor, with the immunotherapy drug **durvalumab (Imfinzi)** in patients with advanced solid tumors who harbor *BRCA* mutations. By number of prior lines of chemotherapy, the median progression-free survival (PFS) was 11.7 months for patients with 0 or 1 prior lines, and 6.5 months in those with 2 prior lines. Overall, patients exhibiting responses showed durable benefit, with a median duration of response of 9.2 months. For patients with HR+ disease, the median PFS was 9.9 months, and the median overall response rate was 69.2%. In the TNBC group, the median PFS was 4.9 months, and the objective response rate was 58.8%. This combination continues to be tested in patients with triple-negative MBC (NCT04711824, NCT03801369). **From:** ***https://www.targetedonc.com/news/olaparib-plus-durvalumab-show-durable-activity-in-germline-brca-breast-ovarian-cancer*** and ***https://www.targetedonc.com/conference/sabcs-2019/durvalumab-maintenance-may-improve-outcomes-in-triplenegative-breast-cancer***

- **Olaparib (Lynparza), fulvestrant (Faslodex), and palbociclib (Ibrance).** As reported at ASCO 2024 (abstract #10616), data from the Phase 1 HOPE trial (NCT03685331) showed that in patients with BRCA1/2-associated HR+, HER2- MBC, this triplet combination provided an acceptable dose limiting toxicity rate. Complete response, partial response, and progressive disease were seen in 1 patient each, and stable disease was seen in 5 patients. Sequential rather than combination treatment and monitoring of hematologic toxicity may be necessary.

- **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) was 18.8 months, with three patients having a complete response (CR) beyond 3 years. In the Phase 2 trial of **veliparib** alone, the PFS was 5.2 months and the overall survival was 14.5 months. (Only one of 30 patients responded to the combination therapy after progression on veliparib alone). The Phase 3 BROCADE3 trial (NCT02163694) reported that the PFS benefit that was initially observed did not translate into improved OS. **From[197, PMID:28356425]:** ***https://www.ncbi.nlm.nih.gov/pubmed/28356425*** and ***https://www.ejcancer.com/article/S0959-8049(24)00056-X/abstract***

Research and Potential Therapies for Patients with Other Tumor Mutations and Biomarkers

As 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 *P53* and other mutations, some of which have encouraging results.

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 **paclitaxel (Taxol)** had a median overall survival of 20.9 months versus 10.4 months for the 31 patients treated only with **paclitaxel (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 (NCT01953926) sought to evaluate the safety and efficacy of **neratinib (Nerlynx)** in HR+ patients who have solid tumors with activating *HER2* or *HER3* mutations. In the *HER2*-mutant, HR+ positive breast cancer cohort, 47 patients received **neratinib (Nerlynx)** in combination with **fulvestrant (Faslodex)**. In this group, 43 patients (92%) had HER2- 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 **fulvestrant (Faslodex)**. Twenty 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 duration of response was 9.2 months, and the median progression-free survival was 5.4 months. Patients who had received prior **fulvestrant (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:** ***https://cslide.ctimeetingtech.com/breast2019/attendee/confcal/show/session/46#presentation-abstract-5892057785104***

HER2 or *HER3* Mutations in metastatic TNBC: As reported at ASCO 2024 (abstract #1094), data from SUMMIT in a cohort of patients with *HER2*-mutant, metastatic TNBC showed that patients who received **neratinib (Nerlynx)** or **neratinib (Nerlynx)** plus **trastuzumab (Herceptin)** had a median progression-free survival of 2.9 months (neratinib (Nerlynx)) and 6.2 months (neratinib (Nerlynx) plus trastuzumab (Herceptin)).

HER3-Overexpressed MBC Patients: Patritumab deruxtecan (HER3-DXd, U3-1402) is an investigational antibody-drug conjugate (ADC) targeting HER3. Investigators conducted a pooled analysis of patients with HER3-high or HER3-low HR+ HER2- MBC (n = 113); HER3-high TNBC (n = 53); or HER3-high, HER2+ MBC (n = 14). (Investigators defined HER3 high as 75% or greater membrane positivity and HER3 low as 25% to 74% membrane positivity). Patients with HR+, HER2- disease had received a median of 6 prior lines of therapy in the advanced setting. Those with metastatic TNBC had received a median of 2 prior lines, and those with HER+ disease had a median of 5.5 prior lines. For HR+, HER2- patients who had HER3-high or HER3-low cancer, at a median follow-up of 31.9

months, progression-free survival (PFS) was 7.4 months, and overall survival (OS) was 14.6 months. For TNBC patients with HER3-high cancer, the ORR was 22.6%, the median duration of response was 5.9 months, PFS was 5.5 months, and OS was 14.6 months. And in patients with HER2+, HER3-high MBC, the ORR was 42.9%, the median duration of response was 8.3 months, PFS was 11.0 months, and OS was 19.5 months. **From:** ***https://www.onclive.com/view/patritumab-deruxtecan-induces-promising-efficacy-in-her3-expressing-metastatic-breast-cancers*** and ***https://www.daiichisankyo.com/files/news/pressrelease/pdf/202206/20220603_E.pdf***

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 *PIK3CA*, *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.

PALB2* Germline or *BRCA1/2* Acquired Mutations:** As reported at ASCO 2024 (abstract #1021), findings from the Phase 2 TBCRC 048 (NCT02032823) study indicate that MBC patients with germline *PALB2* or somatic *BRCA1/2* mutations may benefit from monotherapy with **olaparib (Lynparza)** treatment. In patients with germline *PALB2* mutations, the median progression-free survival (PFS) was 9.6 months, and in those with a somatic *BRCA1/2* mutation, median PFS was 5.6 months. Identifying predictors of response for patients with a somatic *BRCA1/2* mutation will be important.. **From:** ***https://oncology.medicinematters.com/asco-2020/breast-cancer/olaparib-palb2-brca1-2/18060114#:~:text=ASCO%202020%20%7C%20News-,Olaparib%20breast%20cancer%20activity%20not%20confined,with%20germline%20BRCA1%2F2%20mutations&text=medwireNews%3A%20Findings%20from%20the%20proof,may%20benefit%20from%20olaparib%20treatment and ***https://www.medpagetoday.com/meetingcoverage/ascoexpertroundtablebreastca/110997?xid=nl_mpt_DHE_2024-07-08&mh=a5b163f9bc8ee8a077e31262b4e7fbea&utm_source=Sailthru&utm_medium=email&utm_campaign=Daily%20Headlines%20Evening%202024-07-08&utm_term=NL_Daily_DHE_dual-gmail-definition***

Tumor-infiltrating lymphocytes (TILs): TILs are immune cells found within and nearby tumors. Tumors that contain many TILs are considered “hot” tumors, meaning that they are inflamed and contain immune cells that can attack and kill the tumor cells. In contrast, “cold”

tumors contain few or no immune cells. “Hot” tumors are more likely to respond to immunotherapy than “cold” tumors because the cells that mediate the response to immunotherapy are already present near the tumor. Triple-negative breast cancers typically have more TILs than other subtypes. The presence of TILs in breast cancer is being explored as a biomarker for predicting response to immunotherapy. From: ***https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9913599/pdf/cancers-15-00767.pdf***

36. 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 all patients should consider arranging for palliative care to optimize quality of life while getting treatment, 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, and lack of insurance coverage for opioids. Over the past several years there has been increasing pressure on medical professionals to restrict opioid prescriptions, and insurance companies are increasingly denying coverage for these medications. This in turn has caused many people suffering cancer-related pain and other types of chronic pain to be under-treated. In response to the increasing hesitancy to adequately medicate cancer patients for pain, in 2019 the Center for Disease Control (CDC) issued a letter to three medical societies - the American Society of Hematology, the American Society of Clinical Oncology (ASCO), and the National Comprehensive Cancer Network - indicating that people with severe pain from cancer should not be denied insurance coverage for opioid painkillers, and that the previous guidelines for restricting opioid prescriptions weren't intended to deny opioids to patients suffering from chronic pain. **From:** ***https://medicalxpress.com/news/2019-04-denials-opioid-coverage-spurs-cdc.html***

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**
- **Essential Oils**
- **Low-Dose Naltrexone (Vivitrol)**
- **Muscle Relaxers**
- **Nerve Blocks (including Epidurals)**
- **Over the Counter (OTC) Drugs**
- **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 cause a person to feel pain. Examples include **amitriptyline (Elavil), doxepin (Silenor),** and **nortriptyline (Pamelor).** Additionally, some people experienced a significant decrease in neuropathy-induced pain when they took a prescription antidepressant drug called **duloxetine (Cymbalta).**
  From[198, 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[198, PMID:26141332]: ***http://www.mayoclinic.org/diseases-conditions/peripheral-neuropathy/basics/treatment/con-20019948***
- **Essential oils:** A recent analysis of six studies on aromatherapy showed essential oils reduced pain intensity. However, the study also called for more preclinical and well-designed clinical trials. **From:** ***https://pubmed.ncbi.nlm.nih.gov/37108246/***
- **Low-Dose Naltrexone (Vivitrol)**. **Naltrexone (Vivitrol)** is an opiate antagonist currently available in a daily 50-mg tablet dose for the treatment of alcohol and opioid dependence. But in addition to opioid receptor antagonism, the drug also appears to exert

anti-inflammatory effects via a separate mechanism targeting microglial cells (cells found in the central nervous system [CNS] that remove damaged neurons and infections and are important for maintaining the health of the CNS). Paradoxically, the **naltrexone (Vivitrol**) dosage found to reduce pain is roughly one-tenth the substance abuse treatment dose, around 4.5 mg per day. The low-dose version is not approved by the FDA and must be specially compounded. In studies of several known inflammatory conditions, including inflammatory bowel disease and multiple sclerosis, LDN reduced both self-reported pain and objective markers of inflammation and disease severity. Dr. Bruce Vrooman, an associate professor at Dartmouth's Geisel School of Medicine, stated that with regard to treating some patients with complex chronic pain, low-dose **naltrexone (Vivitrol**) appears to be more effective and well-tolerated than the big-name opioids that dominated pain management for decades. (That said, the use of low-dose **naltrexone (Vivitrol)** in cancer patients with chronic pain warrants further study). **From:** ***https://www.medscape.com/viewarticle/894020***

- **Muscle Relaxers**: Muscle relaxers such as **cyclobenzaprine (Flexeril)** 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, or “intrathecal drug delivery” system, 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.

Two recent meta-analyses showed that pain pumps significantly decreased cancer pain and the amount of opioids patients took. **From:** ***https://pubmed.ncbi.nlm.nih.gov/35422368/*** and ***https://pubmed.ncbi.nlm.nih.gov/35088743/***

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 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 **[199, 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.

Acupuncture and massage. The IMPACT study compared acupuncture with massage to treat pain in 298 advanced cancer patients. They found that both treatments reduced pain with no statistical difference in reduction between massage and acupuncture. Additionally, fatigue and insomnia were both improved by both

treatments. The authors conclude that "Integrating these non-pharmacological therapies into comprehensive cancer care can improve symptom management and quality of life for the ever-growing number of patients living with advanced cancer as a chronic illness." **From:** ***https://ascopubs.org/doi/10.1200/JCO.2023.41.16_suppl.12101***

CBD/THC: In Sept. 2020, the Global Task Force on Dosing and Administration of Medical Cannabis in Chronic Pain issued the recommendations bulleted below, stating that health care providers have previously refrained from using medical cannabis to treat pain because there have been no accepted guidelines about dosing and administration. They recommend starting with CBD in most cases because they have observed patients benefiting solely from CBD, which - unlike THC - does not have psychoactive properties. The task force encourages health care providers to consider medical cannabis for patients dealing with inflammatory, nerve-related, and mixed pain.

- Treat the majority of patients by starting them with 5 mg of cannabidiol (CBD) twice daily. Tetrahydrocannabinol (THC) should only be introduced if patients do not respond to at least 40 mg of CBD daily, starting with 2.5-mg daily THC doses. THC doses should be capped at 40 mg daily.
- Frail and elderly patients, and those with severe co-morbidities or who are taking multiple medications should be treated via a conservative route. This means starting the THC doses at 1 mg daily and titrating up the THC more slowly.
- Patients suffering from severe pain and those who have significant prior cannabis consumption can start with a CBD-THC balanced dose of between 2.5-5 mg per each compound once or twice daily.

From:
https://www.medpagetoday.com/meetingcoverage/painweek/88593?utm_source=Sailthru&utm_medium=email&utm_campaign=Weekly+Review+2020-09-20&utm_term=NL_DHE_Weekly_Active&fbclid=IwAR2CpWHkIMg1gp07_8_PVSFSIe5OkHK3pntLIvF82gE4WQmrEwW4w6nwac0

A recent quantitative review of the literature that extracted data from 65 placebo-controlled studies found that cannabinoids did not reduce acute or cancer pain, but did reduce chronic pain. Overall cannabinoid use was not associated with serious adverse events, but was associated with non-serious adverse events. The authors did find that cannabinoids increased quality of sleep but did not affect quality of life. **From:** ***https://pubmed.ncbi.nlm.nih.gov/36716312/***

Another recent quantitative review focused on oral CBD/THC and found moderate-to-low evidence for a lack of pain control. **From:** ***https://pubmed.ncbi.nlm.nih.gov/37283486/***

A good resource for those interested in cannabinoid use is the American Cannabis Nurse's Association https://www.cannabisnurses.org/. Also, be aware that efficacy and side effects can vary from person to person and may be especially different in the neurodivergent population.

Exercise: Two reviews analyzing multiple randomized controlled trials found exercise reduced pain in cancer patients. Most exercise programs included aerobic and strength training. **From:** ***https://pubmed.ncbi.nlm.nih.gov/37039883/*** and ***https://pubmed.ncbi.nlm.nih.gov/36882538/***

Additionally, a 2023 meta-analysis of 13 studies provided support for exercise to reduce symptoms and deep sensitivity of chemotherapy-induced peripheral neuropathy. **From:** ***https://pubmed.ncbi.nlm.nih.gov/36972017/***

As reported at SABCS 2023 (GS02-10), the PREFERABLE-EFFECTS study on exercise specifically in MBC patients showed that a combination of supervised aerobic, strength, and balance training led to decreased pain. **From:** ***https://www.h2020preferable.eu/***

It is important to speak with your doctor before beginning any exercise program.

Massage: In a review of 13 randomized control trials, authors found significant reduction in pain for cancer patients who received massage therapy. This was especially true in patients who had 10-30 minutes of massage therapy for more than 1 week. **From:** ***https://pubmed.ncbi.nlm.nih.gov/37417622/*** Additionally, a single randomized control trial found an increasing benefit for pain reduction as massage length was increased up to 60 minutes. However, both 30- and 60-minute duration (compared to 15 min) exhibited decreased pain. Massages were given 2 or 3 times a week for 4 weeks, with no difference in pain reduction between frequencies. **From:** ***https://pubmed.ncbi.nlm.nih.gov/36226676/***

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 diagnosis 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**
- **Infrared Heating Pad**
- **MRIgFU Ablation Therapy (ExAblate)**
- **Loratadine (Claritin)**
- **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**

- **Tanezumab**
- **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:** ***https://www.breastcancer.org/types/metastatic/bone-metastasis*** and ***https://www.yalemedicine.org/news/metastatic-bone-cancer-aorif-procedure***

- **Calmare Scrambler Therapy:** Although controversial, 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 may 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, and some 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.
- **Loratadine (Claritin):** Nearly a third of people given pegfilgrastim (Neulasta) injections to increase white blood cell counts experience bone pain, and some MBC patients who are taking pegfilgrastim (Neulasta) reported that loratadine (Claritin) has helped relieve pain.

- **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[200, PMID:24760791]:** ***http://www.sciencedaily.com/releases/2013/06/130602144337.htm***

- **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.

- *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, 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***

  A recent Phase 2 study of 160 cancer patients at MD Anderson concluded that a single high dose of SBRT is more effective and durable than standard multi-fraction radiotherapy (MFRT) for alleviating pain from bone metastasis and reducing opioid use.

  Patients in the trial, who had MBC or other forms of cancer, were required to have painful bone lesions and a life expectancy of more than 3 months. Those who had already received radiotherapy to the target lesion, had a bone fracture at the target site, or who had received radioactive isotope therapy one month prior were excluded.

The study's primary endpoint was pain response measured by a combination of worsening pain scores and an increase in opioid use. The pain response for single-fraction SBRT compared with MFRT was superior, as follows:

- 3 months: 38% response to SBRT vs. 21% response to MFRT
- 9 months: 21% response to SBRT vs. 15%, response to MFRT

Local progression-free survival was better with single-fraction therapy at years 1 and 2, and rates of re-irradiation were numerically lower with SBRT (0% at years 1 and 2) compared with MFRT (3.3% and 5.3% at years 1 and 2. Median overall survival was similar between the two groups, and there were no significant differences in toxicities.

In a subset analysis by radiation dose in the SBRT group, the 16-Gy fraction yielded significantly better pain reduction than 12 Gy at both 3 months (62% vs 30%) and 9 months (42.9% vs 13.3%).

The researcher suggested that patients who have oligometastases receive a full ablative dose of SBRT instead of the 12- or 16-Gy dose, and that patients who have multiple bone metastases and a good performance status should receive a single-fraction SBRT (12 or 16 Gy) dose. **From:** ***https://www.medpagetoday.com/radiology/therapeuticradiology/79513?fbclid=IwAR2TubWn9Z_wwejZzU5RGr-GpqlbfeWxhVHXe_PcjrNx5yQ9AJzDu-Akb_k***

A Canadian study further supported the superiority of SBRT over conventional radiation therapy (CRT) for bone pain relief. The study randomized 229 patients with painful spinal mets to receive either two SBRT fractions for a total dose of 24 Gy, or five CRT fractions for a total dose of 20 Gy. After 3 months, 35% of patients in the SBRT arm of the trial, compared to 14% of those in the CRT arm, reported a complete response rate (no remaining pain from their lesions). Patients continued to be pain free for up to 6 months, when the study concluded, with 32% of those in the SBRT arm reporting no pain compared to 16% of those in the CRT arm. **From:**

https://medicalxpress.com/news/2020-10-spinal-metastases-higher-doses-pain.html

- *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[201, 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 that 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[202, 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**: ***https://www.mayoclinic.org/drugs-supplements/strontium-chlorid***

e-sr-89-intravenous-route-injection-route/description/drg-20066127

- **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 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.

- **Tanezumab.** Data from a Phase 3 clinical trial showed a decrease in pain compared to placebo; however, there were more joint safety events in the tanezumab group compared to placebo. Additionally, tanezumab had more side effects (74% of people vs 69%). The authors stated the need for longer-term follow-up. More research is needed. **From:** ***https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/37343145/***

- **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 **methocarbamol (Robaxin)** was praised by one patient with bone pain. **Methocarbamol (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**
- **Celecoxib (Celebrex)**
- **Curcumin**
- **Duloxetine (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**
- **Tart Cherry Concentrate**
- **Walgreens Extra Strength Muscle Rub**

- **Acupuncture and Electroacupuncture** may often be 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[203, PMID:22965186; 204, PMID:24210070]:** ***http://www.health.harvard.edu/blog/acupuncture-is-worth-a-try-f***

or-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:** Although controversial, 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 may be effective at reducing pain symptoms in some 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***

- **Celecoxib (Celebrex):** One person reported pain relief with a daily dose of 200 mg **celecoxib (Celebrex),** a nonsteroidal anti-inflammatory drug used to treat pain or inflammation

- **Curcumin/Turmeric:** Curcumin, which has 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[205, 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[149, PMID:12097302]:** ***http://www.ncbi.nlm.nih.gov/pubmed/12097302***

- **Duloxetine (Cymbalta):** Several patients who experienced joint pain from AIs reported a significant decrease within days after beginning to take a prescription antidepressant drug called **duloxetine (Cymbalta)**, even on a reduced dose as low as 20 mg.

- **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[206, PMID:25452437]:** ***http://medicalxpress.com/news/2014-12-eases-arthralgia-aromatase-inhibitors.html***

- **Glucosamine HCl 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** 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[207, PMID:15336336]**

- **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 [208, PMID:20664124]**
- **"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 she 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.
- **Tart Cherry Concentrate:** In a randomized, double-blind placebo-controlled study of 48 non-metastatic breast cancer patients suffering pain from aromatase inhibitors, it was determined that the 23 patients in the tart cherry group had a 34.7% average decrease in pain compared with the 25 patients in the placebo group who had only a 1.4% decrease in pain after 6 weeks. (The tart cherry concentrate consisted of one ounce of tart cherry concentrate [equivalent to 50 tart cherries] in 8 ounces of water daily). **From:** ***https://meetinglibrary.asco.org/record/177088/abstract***

- **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 Gel, Cream, or Patch**
- **Compression**
- **Exercise**
- **Gabapentinoids**
- **Herbs**
- **Infrared Heating Pad**
- **Lidoderm Patches**
- **Massage**
- **Milkweed Balm**
- **Nerve Repair Optimizer**
- **Neuropathy Support Formula**
- **Penetrex** and other topicals
- **Physical Therapy**
- **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[209, 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[210, 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:** Although controversial, 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 may 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 Gel, Cream, or Patch** contains an ingredient found naturally in hot peppers that can cause modest improvements in pain from 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. **Capsaicin** is approved in the EU for CIPN. In the US, an 8% capsaicin patch is approved for peripheral neuropathic pain caused by diabetes but not chemotherapy-induced peripheral neuropathy. **From:** ***https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8236465/*** and ***https://pubmed.ncbi.nlm.nih.gov/33905384/***

- **Compression.** For prevention of CIPN, compression therapy was compared to cold therapy versus placebo in a total of 63 patients. Of the two interventions, only compression therapy showed a decrease in CIPN symptoms. **From:** ***https://pubmed.ncbi.nlm.nih.gov/38060077/***

- **Exercise:** Up to 60% 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***

- **Gabapentinoids**. There is an ongoing clinical trial to study oral **gabapentin** to prevent paclitaxel-induced peripheral neuropathy. (***https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-023-07126-1***) A **gabapentinoid**, **mirogabalin**, was given to 52 patients receiving oxaliplatin or taxane-based chemotherapy. CIPN pain was reduced by an average of 30% in all patients and 40% in those with more severe CIPN. The most commonly reported side effect in 14% of patients was drowsiness. A total of 31% had some adverse reaction to the treatment. **From:** ***https://bmccancer.biomedcentral.com/articles/10.1186/s12885-023-11560-4#Sec11***
- **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.

- **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 results using this, and some use it in conjunction with Neuropathy Support Formula (immediately below).

- **Neuropathy Support Formula:** Several patients have claimed to have good results using this, potentially in conjunction with Nerve Repair Optimizer (above).

- **Penetrex** and other topicals such as **Blue Emu** are reputed to help ease discomfort from neuropathy.

- **Physical Therapy** may in some instances help alleviate neuropathy-induced pain.

- **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 to 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[198, 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 **vinorelbine (Navelbine)**. The solution that 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.

Therapies For Taxane-Associated Acute Pain Syndrome

Taxanes are a group of cytotoxic chemotherapy drugs that includes **paclitaxel (Taxol, Abraxane)**, **docetaxel (Taxotere)**, and others. The majority of patients who take these drugs experience some sort of muscle and/or joint pain starting around day two and lasting up to a week after each infusion. Treatment recommendations include **ibuprofren (Advil)** as a first-line treatment, and if that is ineffective, a small study showed that low-dose steroids (10 mg prednisone twice daily) were effective at mitigating pain in most patients. **From:** ***https://www.sciencedirect.com/science/article/abs/pii/S009082589895226X*** Other drugs that may have some effectiveness include **gabapentin, loratidine (Claritin)**, and the supplement **glutamine**. **From:** ***https://jhoponline.com/issue-archive/2017-issues/jhop-june-2017-vol-7-no-2/17180-a-taxing-consequence-taxane-acute-pain-syndrome***

One patient has found heat to be an effective relief whether in the form of a hot bath or a heating pad and blanket.

37. 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[211, PMID:23647408]:** ***http://www.scientificamerican.com/article/can-acupuncture-treat-depression/***

- **Cognitive-Behavioral Therapy (CBT)** 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[207, PMID:15336336]**

- **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[212, 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 a 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.

- **Support Groups,** whether face-to-face, telephone, or over the Internet, may help to enable people suffering from depression to feel less alone. There are many other places to find support groups. Facebook support groups can be found by searching "metastatic breast cancer support" and include a variety targeted to various needs from general, to newly diagnosed, to treatment specific groups. METAvivor provides in person peer to peer support groups as do many local hospitals and Cancer Support Community. You can find MBC mentors through Project Life (***https://www.projectlifembc.com/https://www.lbbc.org/community/breast-cancer-helpline***) and telephone support through LBBC (***https://www.lbbc.org/community/breast-cancer-helpline***). You can search for support groups here: ***https://www.mbcalliance.org/search-member-programs-resources/***. See also ***METAvivor.org/support*** and ***https://www.facebook.com/groups/288605145721462/?ref=share_group_link***. This list is not comprehensive, but is meant to give

you an idea of the type of groups that exist and where you might find them.

Below is a list of additional online support groups. Please note that the authors cannot guarantee the quality of the group or that it is moderated well.

General Peer Support – MBC specific

- Closed Metastatic (Stage IV) Breast Cancer Support Group o Closed (Stage IV) MBC Support Group
- Living Metastatic One Day At A Time (MBC Only) o Living Metastatic One Day At A Time
- MBC Advocacy and Support – open to all stages and allies o MBC Advocacy and Support - open to all stages and allies
- Thriving with advanced metastatic stage 4 breast cancer o Thriving with advanced metastatic stage 4 BC
- Care, Compassion, Comfort: The Closed MBC Group o Care, Compassion, Comfort: The Closed MBC group
- Metastatic Breast Cancer – Living Life and Thriving o MBC - Living Life and Thriving
- Komen Metastatic Breast Cancer (Stage IV) Group o Komen MBC (Stage IV) Group
- Metastatic Breast Cancer Advocacy Group Open to Stages 9,1,2,3 & 4 o MBC Advocacy Group Open to stages 0,1,2,3 & 4
- MBC De Novo Ladies Support Group o MBC De Novo Ladies Support Group
- De Novo Stage 4 Breast Cancer o De Novo Stage 4 Breast Cancer

Topic-Specific MBC Facebook Groups

- Oligometastatic Breast Cancer (OMBC) Info and Support o Oligometastatic Info & Support Group
- BRCA Strong – 3k+ members (****not MBC specific)** o BRCA Strong - for those with BRCA mutations (ALL stages)

- BRCA1 & BRCA2 support group (ALL stages) o BRCA1 & BRCA2 FB group (ALL stages)
- Metastatic Breast Cancer – An honest discussion about living & dying with MBC o MBC - honest discussion about living & dying
- PIK3CA Pathbreakers o PIK3CA Pathbreakers - for MBC patients with PIK3CA mutation
- Advocating for Supportive Care o Supportive/Palliative Care Support group (ALL stages)
- Managing depression and anxiety while living with MBC o Managing depression and anxiety while living with MBC
- Breast Cancer Financial Assistance Stage IV o Financial Assistance Stage IV (MBC)
- Finding HUMOR After Breast Cancer (The Original!) (ALL Stages) o Finding Humor after BC Diagnosis (All stages)
- MBC Grieving Together o MBC Grieving Together
- Stage IV Breast Cancer Truths o Stage IV Breast Cancer Truths
- MBC Cheer Group – Stage 4 BC Sisters Cheer One Another with Greeting Cards o MBC Cheer Group - Stage 4 (Cheer One Another with Greeting Cards)
- Active with MBC o Active with MBC
- Making Our Best MBC Life o Making Our Best MBC Life
- Momming with mets support o Momming with mets support
- Cancer Self-Care Support Group (has regular Zoom meetings/presentations and includes more than just MBC patients, but is run by an MBC patient) o Cancer Self Care Support Group
- Social Security Disability Guidance for SSI & SSDI o Social Security Disability Guidance
    - Stage 4 (metastatic) breast cancer Christian Support Group Stage 4 (metastatic) Christian based FB support group

Subtype Specific MBC Facebook Groups

- Triple Negative BC Stage 4 o TNBC Stage 4 FB Peer Support Group
- Support for People w/ Metastatic (Stage 4) Lobular Breast Cancer o Support for People w/ Metastatic (Stage 4) Lobular Breast Cancer
- Hormone Positive Breast Cancer Support (all stages) o Hormone Positive Breast Cancer Support

Treatment (MBC) Specific Facebook Groups

- Enhertu (DS-8201A) o Enhertu (DS-8201A)
- Metastatic Breast Cancer Survivors on Ibrance & Faslodex therapy o MBC Survivors on Ibrance & Faslodex therapy
- Taxol (Paclitaxel) (Onxal), Taxotere, Abraxane for Metastatic Breast Cancer o Taxol (Paclitaxel) (Onxal), Taxotere, Abraxane for MBC
- Metastatic BC Ibrance, Kisqali, Verzenio Group (CDK4/6 inhibitor) o Metastatic BC Ibrance, Kisqali, Verzenio Group (CDK4/6 Inhibitor)
- Xeloda/Capecitabine Stage 4 – Metastatic Cancer Support Group o Xeloda/Capecitabine Stage 4 - Metastatic Cancer Support Group
- Kadcyla for Metastatic Breast Cancer o Kadcyla for MBC
- Piqray and those with PIK3 mutations Support group o Piqray and PIK3 mutations

Treatment-Related Side Effects / Metastatic Site Specific Groups

- Living with Osteonecrosis of Jaw o Living with Osteonecrosis of Jaw
- Surgical Menopause Support Group (Surmeno Connection) o Surgical Menopause Support Group
- Brain Mets in MBC + Christine o Brain Mets in MBC + Christine
- People living with Bone Mets Group o People with Bone Mets Group

Research/Scientific MBC Facebook Groups

- MBC trials and innovative treatments- o MBC trials and innovative treatments

NEW

- Caregivers/spouses/partners of those living with MBC caregivers/partners/spouses facebook support group

Organization related

- Breast Cancer Support: All Ages, All Stages o LBBC All Ages, All Stages Peer Support Group (Living Beyond Breast Cancer)
- Project Life – Insiders (must be a Project Life MBC member) o Join Project Life MBC
    - Members Only Project Life Insiders FB group
- SABCS Patient Advocates – for advocates attending the San Antonio Breast Cancer Symposium o SABCS Patient Advocates (attending SABCS virtual or in person)
- NBCC Policy Advocates (public group) o NBCC (National Breast Cancer Coalition) Policy Advocates - public group
- METAvivor Volunteers (for trained METAvivor Peer Support volunteers) o METAvivor Volunteers FB group (for trained volunteers & #LightUpMBC)
- YSC – Just for Stage IV: Support For Young Mets Thrivers o YSC -- Just for Stage IV: Support For Young Mets Thrivers
- FORCE Hereditary Cancer Community (www.facingourrisk.org) o FORCE Hereditary Cancer Community
- Shades of Brown Foundation o Shades of Brown Foundation
- Breast Cancer Baddies: A breast cancer community for women of color o Breast Cancer Baddies: A breast cancer community for women of color

Local/Regional/State MBC FB Peer Support groups

FLORIDA

- Florida Stage IV MBC Peer Support Group o Florida MBC Peer Support Group

- SWFL Peer-To-Peer MBC Support Group o SWFL MBC Peer Support Group
- Sarasota/Manatee METAvivor Peer-to-Peer MBC Support Group o FL Sarasota/Manatee County MBC Peer Support Group
- Metastatic Breast Cancer South Florida o Metastatic Breast Cancer South Florida

COLORADO

- Colorado Stage IV MBC Peer Support Group o Colorado Stage IV MBC Peer Support Group

NORTH CAROLINA

- Piedmont Triad METsters (NC) Peer Support Group o **Piedmont Triad METsters (NC) Peer Support Group**

NORTH CAROLINA / SOUTH CAROLINA

- **o** Living With MBC – NC & SC Peer Support **Living With MBC - NC & SC Peer Support**
- Charlotte Metsters o **Charlotte Metsters FB Group**

- **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 (Nolvadex)** 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 (Novadex) Interactions: Some antidepressant drugs can interfere with the body's ability to process **tamoxifen (Nolvadex)** effectively. *Patients taking **tamoxifen (Nolvadex)** should preferably **not** be given the following drugs or supplements* for depression unless a viable reason is provided by their doctor.

Bupropion (Wellbutrin)
Duloxetine (Cymbalta)
Fluoxetine (Prozac)
Hypericum (Saint John's Wort)
Paroxetine (Paxil)
Sertraline (Zoloft)

The following drugs are of lower risk, or have not been well-studied:

Citalopram (Celexa) – Slight risk of interaction with **tamoxifen (Nolvadex)**

Desvenlafaxine (Pristiq) – There may be a slight risk of interaction with **tamoxifen (Nolvadex)**, although it has not been well studied.

Escitalopram (Lexapro) – Slight risk of interaction with **tamoxifen (Nolvadex)**

Mirtazapine (Remeron) – There may be a slight risk of interaction with **tamoxifen (Nolvadex),** although it has not been well studied.

From[213, PMID:20141708]: ***https://www.verywell.com/antidepressants-that-interact-with-tamoxifen-430175***

Categories of Antidepressants are:

- **Atypical Antidepressants**
- **Benzodiazepines**
- **BuSpar**

- **Monoamine Oxidase Inhibitors (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 **alprazolam (Xanax), clonazepam (Klonopin), diazepam (Valium)**, and **lorazepam (Ativan)** 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)**: 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. A novel fast-acting nasal spray called **Esketamine (Spravato)** was FDA-approved in 2019 to treat depression in adults who have tried other antidepressant medications without success. **Esketamine (Spravato)**, which acts somewhat as a dopamine reuptake inhibitor, is specifically intended for people with major depressive disorder who have tried at least two antidepressants and haven't responded to treatment (known as treatment-resistant depression).

- **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[214; 215, PMID:20041476; 216, 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!*" **Author's note: Venlafaxine (Effexor)** should not be taken by patients being treated with **tamoxifen (Nolvadex)**. **From:** ***https://www.medpagetoday.com/meetingcoverage/sabcs/36392***

38. Therapies to Reduce Fatigue and Insomnia

Cancer-related fatigue 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 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 UTIs. 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 <u>not</u> 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 and long-term disability 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**
- **Psilocybin**
- **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[217, 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[218, 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 650-mg 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[207, PMID:15336336]**

- **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[212, 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[219, PMID:21056846]:** ***http://www.ncbi.nlm.nih.gov/pubmed/21056846***

- **Psilocybin:** At least two studies have been conducted on psilocybin-based therapy for advanced cancer patients. In both studies, psilocybin led to a decrease in anxiety and depression, including anxiety surrounding death. The benefit appears to persist for at least 4.5 years in 60-80% of patients in one long-term follow-up. Note that psilocybins are not legal in all states, and both studies were conducted under the care of a trained specialist. ***https://journals.sagepub.com/doi/10.1177/0269881119897615?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed*** and ***https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5367557/***
  Another great resource for information on psilocybins for MBC patients is the Our MBC Life Podcast, which did a few episodes on psilocybins. ***https://www.ourmbclife.org/search?q=psilocybin***

- **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 acknowledgement 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, such as **Provigil** and **Ritalin**, may alleviate cancer-related fatigue **From[220, PMID:18053430; 221, PMID:18695134]:**
  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**
- **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. A sham control clinical trial showed that acupuncture decreases the use of sleeping medications. In another study, quality of sleep was improved significantly compared to standard of care.
  From[222, PMID:19922248]: ***http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3156618/*** and ***https://pubmed.ncbi.nlm.nih.gov/37101228/*** and ***https://pubmed.ncbi.nlm.nih.gov/36989257/***

- **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[223, 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[224, 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[212, PMID:25132206]: ***http://www.ncbi.nlm.nih.gov/pubmed/25132206***

- **Reading before bed** may help some people to relax.
- **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:
  https://www.health.harvard.edu/blog/can-blue-light-blocking-glasses-improve-your-sleep-202110262625

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 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)
Eszopiclone (Lunesta)
Flurazepam (Dalmane)
Lorazepam (Ativan)
Oxazepam (Serax)
Prazepam (Centrax)
Quazepam (Doral)
Temazepam (Restoril)
Triazolam (Halcion)
Zaleplon (Sonata)
Zolpidem Tartrate (Ambien, Intermezzo)

Much of the above information is **From[226, PMID:19581220; 227, PMID:24733803; 228, PMID:15014609]:** ***http://my.clevelandclinic.org/health/diseases_conditions/hic_Cancer_Overview/hic_Cancer-Related_Fatigue*** and ***http://chemocare.com/chemotherapy/side-effects/sleep-problems.aspx***

39. 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-HT)** 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-HT receptor antagonist, a **neurokinin (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 **ondansetron (Zofran)**, 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 **ondansetron (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[207, PMID:15336336]**

- **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 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. The American Society of Clinical Oncology (ASCO) recently provided guidance for use of cannabis and/or cannabinoids in cancer patients. Their only recommendation is for chemotherapy-induced nausea and vomiting, where they found that cannabis and/or cannabinoids may reduce these side effects when used with ASCO-recommended

anti-emetic therapies. You can find the complete guidelines here ***https://ascopubs.org/doi/10.1200/JCO.23.02596***.

- **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), **Rolapitant (Varubi),** and **NEPA or Netupitant (Akynzeo). 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. **Rolapitant (Varubi)** is an oral drug that was FDA-approved in 2015. **NEPA or Netupitant (Akynzeo)** is a "combination" drug composed of the 5-HT receptor antagonist **palonosetron (Aloxi)** plus an NK1 antagonist. In a randomized clinical trial, fosaprepitant was given on days 1 and 3 versus only day 1 after chemotherapy known to induce vomiting. When given on days 1 and 3, fosaprepitant decreased nausea by about half compared to the day 1 only group. It also slightly decreased vomiting. There was no difference in side effects between the groups. **From:** ***https://bmccancer.biomedcentral.com/articles/10.1186/s12885-023-11070-3***
- **Olanzapine:** This is an antipsychotic drug with relatively few side effects. It can be used "off label" to control nausea and is recommended by ASCO for nausea control. Additionally, recent research has shown that a low dose (2.5 mg) may be as effective as higher doses (5-10 mg) with less sleepiness. Taking this drug before bed may also help with this side effect. ***https://society.asco.org/about-asco/press-center/news-releases/olanzapine-reduces-nausea-and-improves-quality-life-patients*** and

https://www.cancertherapyadvisor.com/reports/low-dose-olanzapine-may-be-preferred-for-chemo-induced-nausea-and-vomiting/

- **Serotonin (5-HT) 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 (Aloxi)** 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 (Aloxi)** 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 (Decadron)*** *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[114, PMID:26374485]:** ***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.

40. 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, **dronabinol (Marinol)** improved appetite by 38%. **From:** ***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 **megestrol Acetate (Megestrol**) and **Medroxyprogesterone** have been associated with appetite stimulation and weight gain. Studies

suggest improved effectiveness in patients with better digestive function. 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). Additionally, studies in Japan have found anamorelin to be beneficial in cachexia patients. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9939183/. As of February 2024, **anamorelin** is approved for use in Japan but not the United States, Europe, or Canada. Currently, there is a double-blind, placebo-controlled study of **anamorelin** for anorexia in people with small cell lung cancer ongoing in New Zealand. https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0285850

41. 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.

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**

<u>The following tend to work mainly when there is a deficiency:</u>

- **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:** ***https://pubmed.ncbi.nlm.nih.gov/23800380/***
- **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 brown rice, broccoli, brussels sprouts, spinach, chickpeas, fortified cereals, liver, egg yolk, beans, almonds, sweet potato, whole grain 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[229, 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 protein 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[230, PMID:23301732]: *http://www.drugs.com/health-guide/vitamin-b12-deficiency.html***

THERAPIES FOR LOW PLATELET COUNTS ("THROMBOCYTOPENIA")

Often the first sign of low platelet counts is a bloody nose, so patients experiencing this issue are encouraged to report it to their doctor.

- **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[231, PMID:20620439]**

- **Papaya Leaf may help boost platelet counts.** One person on an online MBC forum wrote that she brewed dried papaya leaves 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."

There are 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[232, 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** may 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**). **Darbepoetin alfa (Aranesp)** is a unique, longer-acting form of erythropoietin and is more convenient because it allows patients to receive fewer injections than with **Epoetin alfa (Epogen/Procrit).**

From[231, PMID:20620439]

Warning: Before a patient can begin taking the above medications, they must sign an acknowledgement 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 **filgrastim (Neupogen)**, and **pegfilgrastim (Neulasta)**. 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 **pegfilgrastim (Neulasta)** was proven to be as effective as an average of 11 daily injections of **filgrastim (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/***
  It's important to speak with your oncologist about vaccines as they can protect you against some infectious diseases that can cause a lot of harm or even death when your white blood cell count is low (this is known as being "immunocompromised"). Additionally, you should ask about which specific vaccines you can receive, as some vaccines may not be appropriate when you are immunocompromised (for example, live vaccines). For more information on vaccinations during cancer treatment from the American Cancer Society, see this link ***https://www.cancer.org/cancer/managing-cancer/side-effects/low-blood-counts/infections/vaccination-during-cancer-treatment.html***

42. 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.
- **Electroacupuncture for opioid-induced constipation**. In a randomized, sham control trial of 100 patients, electroacupuncture slightly increased the number of bowel movements per week (average of 0.6) compared to the sham control. However, this was not consistent for every week of the 24 weeks the study was conducted. No effects were seen on cancer pain or opioid use. Side effects were comparable between the two groups and included local hematoma (4%) and "inconsequential bleeding" (2%). From: ***https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2801734***

- **Kiwifruit**. When compared to psyllium (fiber ingredient in Metamucil), consuming two kiwifruit a day increased bowel movements and improved GI comfort. This was a randomized, controlled trial with 184 patients. **From:**

https://journals.lww.com/ajg/fulltext/2023/06000/consumption_of_2_green_kiwifruits_daily_improves.26.aspx

- **"The Bomb" Recipe:** Combine 1 cup high fiber bran cereal, one 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)
Coconut oil (one teaspoon in a hot beverage daily)
Docusate sodium (Colace)
Glycerin suppository
Lactulose (Kristalose, Enulose, Constulose, and Generlac), a prescription medication.
Linzess (a prescription medication)
Lubiprostone (Amitiza), a prescription drug used to treat chronic constipation, or constipation caused by opioid pain medicine
Miralax
Psyllium (Metamucil)
Magnesium citrate
Magnesium hydroxide (Milk of Magnesia)
Senokot-S, (a less expensive version is Equate Stool Softener Plus Stimulant Laxative)
Smooth Move Tea
Sorbitol and sodium phosphate (Fleet's enema)
Stool softeners
Swiss Kris Herbal Laxative
Traditional Medicinal Herbs Smooth Move Tea

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 **methylnaltrexone (Relistor)** is safe and effective if used for longer than 4 months in people with advanced illness. There is evidence that **methylnaltrexone (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 **methylnaltrexone (Relistor)** for opioid-induced constipation and 112 were given a placebo. 57% of the

patients who received **methylnaltrexone (Relistor)** experienced relief from constipation; 43% did not. Patients who received and responded to **methylnaltrexone (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%). A recent placebo-controlled study in cancer and noncancer patients with OIC found that **methylnaltrexone (Relistor)** led to a greater chance (~60% versus ~20%) of passing a stool in 4 and 24 hours. The estimated time to passing a stool was also shorter. Pain control by opioids was not reduced. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10391063/

Much of the above is **From[235, PMID:25135384; 236, PMID:27857691; 237, PMID:27573565]:** ***http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4108020/***

43. 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. Patients may want to eliminate dairy and wheat products for a little while to see whether that many help.
- **Crofelemer (Mytesi)**. This drug is approved for the treatment of diarrhea caused by HIV therapy (antiretroviral therapy). However, there have been small studies, and a large, Phase 3 placebo-controlled clinical trial of cancer patients receiving targeted therapy (OnTARGET) is ongoing with an expected completion date of April 2024. From: ***https://classic.clinicaltrials.gov/ct2/show/NCT04538625***

- **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.

- Probiotics, prebiotics, and synbiotics. Probiotics are live microorganisms that are ingested in pill form. Many times these are bacteria, but they can also be fungi such as yeast. Prebiotics are non-living, specific food for microbes taken to support the microbes already in the gut or taken with probiotics. Synbiotics are a combination of probiotics plus prebiotics.
  There has been a lot of study of probiotics in antibiotic-induced diarrhea and to a lesser extent, in radiation-, chemotherapy-, and chemoradiation-induced diarrhea. Quantitative reviews of the research have found that probiotics can lead to less diarrhea, but the data seem to support this mostly in higher grade or worse diarrhea (greater than or equal to grade 2). **From:** ***https://www.sciencedirect.com/science/article/pii/S1743919120307482?via%3Dihub and https://pubmed.ncbi.nlm.nih.gov/31783578/***
  Additionally a recent study found that abemaciclib (Verzenio)-induced diarrhea was improved by probiotics, but only severe diarrhea (grade 3). The study was also small. ***https://pubmed.ncbi.nlm.nih.gov/37459790/***
  There are many unknowns regarding probiotics. First, there are varous different formulations of probiotics (with different bacteria for example), which makes drawing conclusions from research studies difficult. Additionally, probiotics in the US are not well regulated leading to difficulties in knowing which probiotic to take and how effective it will be. These probiotics can also lead to other gastrointestinal effects (reduced bloating for example), though

rarely adverse. Use of probiotics, prebiotics, and synbiotics is generally a low-risk intervention that can show benefit. However, viability and brand are concerns. Therefore, like any supplement, it's essential to check with your oncologist before taking probiotics or synbiotics and to be aware that each patient's experience may vary.

- **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***

44. Therapies for Hand Foot Syndrome

Hand-Foot Syndrome (HFS), also called Palmar-Plantar Erythrodysesthesia, is a side effect of some chemotherapy drugs – especially **capecitabine (Xeloda)** 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, HFS 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 **capecitabine (Xeloda)**, studies have been done on decreasing the drug's recommended dose and frequency. The current standard dose of **capecitabine (Xeloda)** as monotherapy is 1250 mg/m^2 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/m^2 administered orally twice daily (morning and evening; equivalent to 2,000 mg/m^2 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 **capecitabine (Xeloda)** can be reduced, either when used alone or in combination with **docetaxel (Taxotere)**, to minimize adverse events without compromising efficacy in terms of time to progression or overall survival. **From[46, PMID:21856245]**

Non-drug remedies for HFS 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**
- **CeraVe SA**
- **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**
- **Reconval B6 Cream**
- **Shoes that are Very Comfortable!**
- **Topical Heparin**
- **Topical NSAIDs (non-steroidal anti-inflammatory drugs)**
- **Urea Cream (10%)**
- **Vitamin B6**
- **Vitamin E**

- **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.
- **CeraVe SA** is a moisturizer containing salicylic acid that gently exfoliates dry, scaly, or rough and bumpy skin.

- **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: *Mix 1/4 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 (Abraxane), docetaxel (Taxotere),** and **doxorubicin (Adriamycin)**) may help prevent HFS.

- **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 HFS, *"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 the 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 use it 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, phosphorus, magnesium, calcium and zinc.
- **Reconval B6 Cream:** This topical cream may reduce skin inflammation caused by radiation or chemotherapy, and help patients who have HFS. It may also soothe dry, cracked, peeling fingertips and blisters on the hands and feet.
- **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.

- **Topical Heparin:** A Phase 2 study determined that topical heparin is highly effective in treating HFS caused by **capecitabine (Xeloda)**. From: https://pubmed.ncbi.nlm.nih.gov/35356259/ A small study was conducted on patients with HFS. 90% of the patients had reduced symptoms of HFS, and response time was about 3 weeks. **From: *https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8958526/***

- **Topical NSAIDS (non-steroidal anti-inflammatory drugs):** The D-TORCH study, a randomized, placebo-controlled study, showed that applying a 1% gel of **diclofenac** (also known as **Voltaren**) twice a day to the hands and feet reduced HFS from 18% to 6.1%

in patients taking **capecitabine (Xeloda)**. This is a preventive measure and should be started as soon as capecitabine (Xeloda) is. Diclofenac (Voltaren) can be obtained by prescription or over the counter. **From:** ***https://ascopubs.org/doi/10.1200/JCO.2023.41.16_suppl.12005***

- **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 HFS during the first 6 weeks of treatment with **capecitabine (Xeloda)**. One patient mentioned that it has been helpful in treating her HFS after it developed. **From[238, 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[239, 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 100 mg of Vitamin E daily**. From[240, PMID:21494409]**: ***http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3076356/***

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 **celecoxib** (**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.

45. 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!).
- One patient noted that putting on compression socks at the beginning of a cramp has helped her.
- 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.

46. 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 **acetaminophen (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)** 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 may not be effective, although there are some exceptions. For example, one patient with ascites claimed that the prescription diuretic drugs Lasix and spironolactone helped her. 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[241, PMID:16473644]**

47. Therapies for Mouth Sores

Patients taking **everolimus (Afinitor)** and/or other cancer drugs may experience mouth sores, which are painful and 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 dividing 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**
- **Gengigel Mouth rinse**
- **KANK-A**
- **Ketamine Mouthwash**
- **Licorice Root (DGL) Wafers**
- **Lysine**
- **Miscellaneous Over the Counter Therapies**
- **Mucosamin Mouth Wash or Spray**
- **Mugard**
- **Organic Honey**
- **Peroxyl Mouth Sore Rinse**
- **Salt/Baking Soda/Water rinse**
- **Toothpaste with Baking Soda**
- **Triamcinolone Topical Cream**

- **Acidophilus:** This is a probiotic, which is 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 **exemestane (Aromasin)** and **everolimus (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). Physicians often prescribe dexamethasone mouthwash for patients taking **everolimus (Afinitor)**. **From[242]:** ***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.

- **Gengigel Mouth rinse:** Gengigel has been reported to soothe inflamed and damaged oral tissue and restore healthy gums.
- **KANK-A** is an oral product designed to treat mouth sores, and one patient confirmed that using it helped enormously against her sores.

- **Ketamine Mouthwash:** A patient with extremely painful persistent mouth sores for whom no other remedies worked indicated that her sores were responsive to ketamine mouthwash, which provided exceptional relief. A study of 30 patients suffering from this condition confirmed the efficacy of ketamine mouthwash for this group of patients. **From:** ***https://www.ncbi.nlm.nih.gov/pubmed/28190158***

- **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**.

- **Mucosamin Mouth Wash or Spray** were developed to help heal areas of oral ulceration and reduce local sensitivity within the mouth.

- **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.

- **Peroxyl Mouth Sore Rinse** is available in most drugstores and has been reported to help prevent and heal mouth sores.
- **Salt/Baking Soda/Water Rinse**: Combine 1/4 teaspoon baking soda, 1/8 teaspoon salt, and 1 cup warm water. Swish in your mouth for 30 seconds and spit out. Repeat three times daily. Also, a **paste** can be made from **baking soda and water** and applied directly to the canker sore.

- **Toothpaste with Baking Soda:** One patient reported that brushing with a baking soda-based toothpaste was helpful for her mouth sores.

- **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 **everolimus (Afinitor)** or another oral drug that may cause mouth sores, they might first consider first coating the mouth with Cool Whip or apple sauce before taking the pill (if the drug is taken orally), and then put the pill inside the Cool Whip or apple sauce (or inside a marshmallow) before swallowing it. Embedding the pill in a piece of marshmallow is reported by patients to be particularly helpful when taking medications that cause mouth sores.

48. Therapies for Osteonecrosis of the Jaw (ONJ)

Bisphosphonate therapy or therapy with **denosumab (Xgeva)** is an important aspect of treatment for patients with bone metastasis. Osteonecrosis of the jaw (ONJ) is a complication related to bisphosphonate and **denosumab (Xgeva)** therapy and has been reported in 3-7% 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 **zoledronic acid (Zometa)** and **denosumab (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 **denosumab (Xgeva)**, patients are encouraged to visit their dentist. At that time, the patient 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 to 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). A small study of 34 patients randomized to receive either 8 weeks of daily subcutaneous injections of teriparatide (Forteo) or a saline solution revealed an increased rate of resolution (45.4% vs. 33.3%) of medication-related osteonecrosis of the jaw lesions in the teriparatide (Forteo) group. Additionally, a higher proportion of patients receiving **teriparatide (Forteo)** (80.0% vs. 31.3%) showed increased bone volume and a reduction in the size of bony defects at 12

months compared with those receiving saline injections. However, the study authors stressed the importance of limiting the cumulative dose of **teriparatide (Forteo)** due to findings from preclinical studies showing an increased incidence of osteosarcoma in rats treated with this medication. **From:** ***https://www.oncologynurseadvisor.com/home/hot-topics/side-effect-management/teriparatide-for-medication-related-osteonecrosis-of-the-jaw/?fbclid=IwAR0OL6wlLMX4lRpyu2U9SsWyynWQTwFAoNPY6jkUDB55pzTzz2Nkb7nWExw***

Individuals 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 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[243, PMID:22923892; 244, PMID:19021059; 245, 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***

49. Therapies for Radiation Damage

When patients undergo radiation therapy, they may experience damage to the skin in the irradiated area or to internal tissue. Therefore, patients who are about to undergo (or who have undergone) 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 RADIATION DAMAGE

- **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**
- **Sucralfate (Carafate)**
- **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[246, 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 the 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.

- **Silver Sulfadiazine (Silvadene) 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 **silver sulfadiazine (Silvadene)** 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!

- **Sucralfate (Carafate)** is an oral prescription medication that is used to heal ulcers, and several patients who have radiation-induced burns in their esophagus indicated that this medication provided symptom relief and promoted healing.
- Using **warm (not hot) water** while bathing will help prevent the skin from feeling more irritated.

50. 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 and also may extend life. As per *Cure Magazine*'s winter 2019 publication, a study of 2,307 records of advanced cancer patients determined that those who received outpatient palliative care survived 4.5 months longer than those who did not.

Therefore, patients should start palliative care early for best results (although it may be requested at any time), and patients should request it from their doctor instead of waiting for their medical team to bring it up. It is important to note that caregivers are also able to receive palliative care.

The American Society of Clinical Oncology (ASCO) has updated their guidelines to state, *"in-patients and outpatients with advanced cancer should receive dedicated palliative care services, early in the disease course, concurrent with active treatment. Referral of patients to an interdisciplinary palliative care team is optimal, and services may complement existing programs. Providers may refer family and friend caregivers of patients with early or advanced cancer to palliative care services."* **From:** ***https://ascopubs.org/doi/10.1200/EDBK_175474#:~:text=Key%20Recommendation,-%E2%80%A2&text=Patients%20with%20advanced%***

20cancer%2C%20inpatient,services%20may%20complement%20existing%20programs.

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***

51. 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, state and other licensure, joint commission or similar 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.

Does the hospice provide a phone number that can be used for after-hour emergencies?

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.alsa.org/als-care/resources/fyi/hospice.html***

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 a 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 and relax on a leaf of our favorite magnolia tree.

All day I thought about this beetle. His seemingly inevitable demise and his astonishing recovery.

For him or her, things could not have appeared bleeker. A cold, damp night followed by a furious paddle in a (thankfully clean) toilet. Followed by an unexpected and dramatic rescue.

In a way, each of us is like this beetle. We "paddle furiously" by educating ourselves, asking questions of our doctors, and getting through each day with incredible determination despite the daunting challenges foisted upon us by this disease.

Like the beetle, we each have courage, and we continue to hold on to hope.

Anne

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53. Glossary

Although not all the terms below have been used in this document, they are commonly found when researching MBC and other diseases.

Accelerated approval: The FDA's Accelerated Approval Program allows for certain drugs that treat serious conditions where there is an unmet medical need to be approved, based upon the results of a "surrogate endpoint" evaluated in studies. A surrogate endpoint is a scientifically accepted sign of efficacy, such as a laboratory test, radiographic image, or physical sign.

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.

Allele: A variant form of a gene.

Alopecia: Hair loss, which can be caused by chemotherapy and hormonal therapy as well as other reasons.

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- MBC patients. There are currently clinical trials underway to test CDK4/6 inhibitor efficacy on HER2+ 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.

Gene: A hereditary unit consisting of a sequence of DNA that occupies a specific location on a chromosome and is transcribed into an RNA molecule that may function directly or be translated into an amino acid chain. Genes undergo mutation when their DNA sequences change.

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-low breast cancer: Breast cancer that is technically HER2- but with a "low" HER2 expression as defined by a score of 1+ on immunohistochemical [IHC] analysis or as an IHC score of 2+ and negative results on in situ hybridization).

HER2+ 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. HER2+ cancer has a score of +3 on immunohistochemical [IHC] analysis or a IHC score of 2+ and positive results on in situ hybridization. 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.

Hippocampus: A small region of the brain that is primarily associated with memory and spatial navigation.

Hippocampus Avoidance (or Hippocampus-sparing) WBRT: A special form of Whole Brain Radiation Therapy that spares the hippocampus (a small region of the brain that is primarily associated with memory and spatial navigation) from being targeted by radiation. HA WBRT is accomplished by using Intensity-Modulated Radiation Therapy (IMRT) to deliver precise radiation doses to a malignant tumor or specific areas within the tumor.

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.

Intensity-Modulated Radiation Therapy (IMRT): An advanced mode of high-precision radiotherapy that uses computer-controlled linear accelerators to deliver precise radiation doses to a malignant tumor or specific areas within the tumor.

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.

Interstitial Laser Ablation (ILA, LA, or LITT): Interstitial laser ablation is an emerging technique to treat primary and metastatic brain tumors that can be hard to reach with conventional surgery. It is performed by drilling a very small hole about the size of a pencil's diameter, inserting a laser catheter into the tumor, and heating it to temperatures high enough to kill the tumor.

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.

LHRH agonists. Luteinizing hormone-releasing hormone (LHRH) agonists (also called LHRH analogs or GnRH agonists) are drugs that: 1) In females, reduce the amount of estrogen in the body by temporarily shutting down the ovaries; 2) In men, lower the amount of testosterone made by the testicles.

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.
Microglial Cells: Cells found in the central nervous system (CNS) that remove damaged neurons and infections and are important for maintaining the health of the CNS.
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.

NCCN (National Comprehensive Cancer Network): The NCCN is an alliance of 28 cancer centers in the US, most of which are designated by the National Cancer Institute as comprehensive cancer centers. It is a non-profit organization which provides cancer guidelines.

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.

Neurotrophins: Neurotrophins are a family of proteins that induce the survival, development, and function of neurons. They belong to a class of growth factors that are capable of signaling particular cells to survive, differentiate, or grow.

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.

NTRK fusion: In TRK fusion cancer, the NTRK gene fuses (joins) with an unrelated gene, causing overexpression of the TRK protein. Genomic alterations, such as NTRK gene fusions, are an ongoing area of focus in cancer research and treatment.

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, Zometa, or Aredia 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. 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 that is used in **FDG PET** scans. 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. Another type of PET scan is **FES PET**, which uses a radiotracer composed of estrogen that emits radiation and highlights estrogen receptor (ER) positive cancer cells to determine whether a lesion may respond, or is responding, to endocrine therapy. This test may be especially useful in detecting ER+ lesions that may respond to endocrine therapy in patients with difficult-to-identify lobular cancer and/or brain metastases.

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: Progression with respect to cancer is considered to be a 20% increase in disease measurement, or the appearance of new lesions.
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 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.

Skeletal Related Events (SREs): SREs are a common and often painful and debilitating complication of bone metastases. SREs include pain, fractures and compression of the spinal cord that requires surgery or radiation. SREs can contribute to a higher risk of death and higher health care costs.

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+ 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.

Surrogate endpoint: A scientifically accepted sign of efficacy, such as a laboratory test, radiographic image, or physical sign. It may be used by the FDA in providing accelerated approval for a new treatment.

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.

Topoisomerase I Inhibitor: A new class of anticancer agents that interrupt DNA replication in cancer cells.

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.

Trk Receptors: Trk receptors are a family of tyrosine kinases that regulates synaptic strength and plasticity in the mammalian nervous system. The common ligands of trk receptors are neurotrophins, a

family of growth factors critical to the functioning of the nervous system.

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.

Tumor Mutational Burden High (TMB-H) Tumors: Tumors containing 10 or more mutations per megabase (the length of a genomic segment).

Tyrosine kinase: An enzyme that acts as an "on" or "off" switch in many cellular functions.

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.

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