The More You Know: Metastatic Breast Cancer

With Dr. Bahareh Bahadini,

National Webinar Transcript

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Melissa Rosen: Thank you so much for joining us tonight. My name is Melissa Rosen. I'm the Director of Training and Education at Sharsheret. You've joined us this evening for a very important conversation about metastatic breast cancer. This evening, we're going to clear up a lot of the myths and the misinformation out there. Understanding what metastatic breast cancer is and is not will benefit anyone impacted by breast cancer, benefit caregivers, and of course, benefit those living with a metastatic diagnosis. If you had any doubt this myth-busting evening was necessary, last week I was listening to the news and heard a news reporter explain that actress, Shannon Doherty, who was recently on the cover of People, not only has breast cancer but now has bone cancer as well. My family thought I was absolutely nuts yelling at the television, and this is just one of the misconceptions we will clear up this evening because thankfully, greater numbers of cancer patients are living long and meaningful lives. And this is also true for those who've been diagnosed with stage four or metastatic cancer.

Our Embrace Program, which you'll hear about more later, illustrates this perfectly. When I began at Sharsheret almost 10 years ago, its focus was really on end-of-life concerns. But today, our Embrace Program consists of so many programs about living well alongside cancer. It's an incredible change to witness and in a relatively short amount of time.

Before we begin, I have a few housekeeping items that we always share. First, I want to thank our sponsors for tonight's webinar. Our sponsors enable us to continue to offer really meaningful programs and thank you tonight to Gilead Oncology and to the CDC, the Cooperative Agreement 191906, again from the Centers for Disease Control and Prevention. This webinar is being recorded and will be posted on Sharsheret's website along with a transcript for you to use as a resource. Participants' names and faces, of course, will not be in the recording. You also have the option this evening to be anonymous if you wish to be. You can turn off your camera and even change the name on your Zoom square. There are instructions in the chat box right now on how to make those changes if you wish to do so.

Again, a reminder specifically to our Embrace community, we invite members of that community, those facing metastatic breast cancer, to stay on at the end of the webinar for an intimate breakout session with our speaker, Dr. Bahadini, and Bonnie Beckoff, our Director of Support Services. We actually received many, many questions through the registration process. And as questions continue to arise through the presentation, please use the chat box and we will address them. I'll be monitoring the chat box for questions and we will address them during the Q&A at the end of the session. As a reminder, Sharsheret has been providing telehealth services to breast and ovarian cancer communities for more than 20 years because cancer is so much more than a physical experience. If you are interested in learning more about our free, confidential, and customized services, please email us or visit our website at sharsheret.org.

Before we welcome Dr. Bahadini, we are so very fortunate to welcome to the screen now Ilene, who is a Sharsheret program participant from Florida. She's here to share her story, and I'm actually going to let her introduce herself as she shares the details of her story. Ilene, thank you so much for being here.

Ilene: You're welcome. Thank you for having me. Like she mentioned, my name is Ilene. I live in south Florida. I am 56 and I have been living with breast cancer for 10 years now, exactly 10 years. I was originally diagnosed in 2013 with early stage breast cancer and after a lumpectomy and radiation, I was considered cancer free and nobody really ever talked to me about the potential of stage four, so I just kind of mosey on with my life. I am married, I have a daughter who's 14 now. When I was first diagnosed in 2013, she was three. So in reality, my daughter has truly never known me without cancer and she knows a little too much about it.

In 2016, we discovered another tumor, and shockingly, it was in the same breast in a different quadrant. And as I was getting ready to go through surgery because we decided I was going to have a mastectomy, a PET scan showed that I had potential cancer in my lungs and a small place on my shoulder. And unfortunately, with the pleural effusion, when they removed the fluid, I had no cancer cells there. So I actually had to have a physical biopsy of the lung and I was officially diagnosed with stage four. And in 2016, you hear the word cancer, I think even now you hear the word cancer and you immediately think you're going to die tomorrow. And everything I Googled, everything I saw told me that it was 22 months, my oncologist told me it was 22 months, and it was pretty scary.

And then I met a lot of women who had been living with it for 5, 10, 15, and even 20 years. I mean I know that those 20 year survivors are outliers, but I keep hoping that that's going to be me. I consider myself very lucky. I'm still on my first line of treatment, which is oral. I don't look like your typical cancer patient, so sometimes people forget that I deal with a lot of fatigue, brain fog. I go to the oncologist one to two times a month for blood work to make sure that I can still continue taking my medication.

Up until May of last year, I was working a very stressful, demanding senior management job, and I was actually, my role was eliminated. So, currently I'm not working, which kind of in one way is a good thing because it gives me some rest and relaxation I guess. But the other thing is that my husband in 2020 was also diagnosed with a very rare cancer. So, it also gave me time to be able to deal with his situation and be a caregiver to him. And financially, it takes a toll, even if you have good health insurance. But I have been with Sharsheret since 2016, and they're the best group I think I've ever met and really have helped me see the positive side of all of this because at the end of the day, I really had no choice in this and you just kind of have to live your life the best that you can.

And for me, like I said, I consider myself lucky. My daughter has had me here for many milestones that I honestly did not think that I would be here for. When she

started karate when she was three years old, if you told me that I would be a mother to a second degree black belt, I would tell you that I wouldn't have ever seen that. So I just kind of live each day as it is and I try not to have cancer in the front of everything, but I'm similar to everybody. When you see the wrong language being used by news reporters, especially about celebrities that are saying that they have breast cancer, now they have bone cancer, that's not even the language that Shannen, I can't say her last name-

Melissa Rosen: Doherty.

Ilene: ... uses. She does use that she has stage four or she has metastatic cancer. So, yeah, thank you. So bad. I get tongue twisted, the brain fog causes vocabulary loss sometimes, but sometimes it's comical because I couldn't remember what kind of shoes I was looking for the other day.

But all in all, I do consider myself lucky. I consider myself lucky that I'm still on my first line of therapy. I've been living with metastatic cancer for seven years, which seven years ago I would've told you that that's not going to be possible. And for the most part, with some minor mobility because of the joint pain, we went to Alaska last summer, we've gone to Yellowstone, we go horseback riding, we are making memories. And to me, that's the most important thing. And if anything, I mean I don't like to say that cancer is a blessing because it surely is not, but I've learned to live with intention and making memories for my kid. Because at the end of the day, when I'm buried, I won't remember I was at her wedding, but she'll remember if I'm not there. So, I'm happy for every milestone I get.

And I guess that's my story in a nutshell. I mean I don't know if I'm an outlier. I don't know if next week they'll tell me that my cancer's progressed, but right now, today I'm still walking and healthy.

Melissa Rosen: Ilene, thank you so much for sharing your story. I truly believe that hearing other people's stories makes it easier to understand difficult information. So, it means so much to all of us tonight to have heard yours and to hear that you may have been dealing with cancer for 10 years, but you are living well, making memories. It's wonderful to hear. So, thank you very much. Okay. As we-

Ilene: You're welcome. And I think it's important for people who just got diagnosed to hear those kinds of stories. Because for me, I thought I was going to die tomorrow and meeting people who were 10, 15 years out made it possible for me in my head to tell me that that was going to be me too.

Melissa Rosen: Yeah, yeah, for sure. For sure. Thank you.

Okay. As we move into the primary presentation, I also want to remind you that Sharsheret is a national, not-for-profit cancer support and education organization and does not provide any medical advice. The information provided

by Sharsheret tonight, as well as our doctor, they are not a substitute for medical advice or treatment for your specific medical condition. So you should not use this information to diagnose or treat a health problem. As always, seek the advice of your physician or a qualified healthcare provider with any questions you may have.

We are so very fortunate to have our speaker here with us today. Dr. Bahareh Bahadini is an Assistant Clinical Professor in the Department of Medical Oncology and Therapeutics research with specialties in hematology oncology, breast cancer, and gastrointestinal cancer. She brought her experience in hematology and oncology to City of Hope in 2014 after more than a decade at North Valley Hematology Oncology Group in Mission Hills, California. Dr. Bahadini's training includes residency at Saint Mary's Medical Center and a fellowship in hematology and oncology at City of Hope, including a year of research investigating genetic factors involved with breast cancer. She received her doctorate from Keck School of Medicine of USC and received her Masters of Science degrees in both pathology and applied physiology at the University of Health Sciences Chicago Medical School. Dr. Bahadini founded and has been actively involved in the Wellness through Awareness Integrative Medicine program at Providence Holy Grail Medical Center since 2007. Welcome, and thank you so much for being with us today. This topic is such an important one.

Dr. Bahareh Bah...: Thank you so much, Melissa, for having me and Ilene, for sharing your story. I'm about to share my screen here and making sure that you guys can all see it.

Melissa Rosen: Yes.

Dr. Bahareh Bah...: Okay, perfect. And I think what Ilene talked about just helped me so much to know how we can actually take this lecture and it can be any way that you want it. I do have quite a bit of information in here. Try to focus on some of the therapies. I know patients that are diagnosed with metastatic breast cancer are generally very interested in knowing what's out there. And I just want to say ahead of time that you, as patients, should always ask your primary team oncologist for help in any situation that you're in, even social help, and to also ask whether a second opinion would be appropriate for you or not. And so don't ever hesitate to get other opinions in this field. We certainly encourage that for our patients.

So, I'm currently a medical oncologist at City of Hope Thousand Oaks office, and in my practice, I see quite a few breast cancer patients, probably about 75% to 80% of my practice is breast and the rest is just general oncology. I decided to put as much information in here, simplified it, and we're probably going to skip some of the slides to save time, but the format is as such that we're going to talk about some facts and statistics and what to expect living with metastatic breast cancer. And then what are the differences between the tumor characteristics and patient characteristics that makes us decide how we decide and formulate a plan of care for a patient. And we're going to focus on some of the therapy options.

So, some of the facts and statistics. Breast cancer is the leading cause of cancer death among women globally and it's the second leading cause in the U.S. Treatment paradigms are changing rapidly and mortality is steadily declining, and this is many thanks to the advances in population screening, early stage treatments, we have better treatment options for early stage disease that actually decreases risk of recurrence of the disease. So, despite the fact that we have many, many options for metastatic breast cancer, early diagnosis still remains or early detection still remains crucial and the most effective treatment for breast cancer or in fact for any other cancer. And it generally provides better prognosis. So when we have a smaller tumor at the time of diagnosis, it significantly lowers the probability of mortality.

So, let's talk about the definition of metastatic breast cancer. And so, stage four breast cancer is when the cancer is actually moving beyond the breast into the nearby lymph nodes or other parts of the body. And so when the cancer moves from one organ to the other organs, and it initially, for example, is lung cancer or breast cancer, it would always remain that cancer, that primary cancer. So even if it travels to the bone or to the lung or brain, it's still considered to be breast cancer, not lung cancer. So when it does travel, it most commonly goes to bones, liver, lung, or it may spread to brain and other organs. So these are just some of the common areas that it can go to. So majority of women with breast cancer, maybe 90%, have already been diagnosed with breast cancer earlier stages, just like Ilene's story, they would be diagnosed with early stage one, two, or even three early on, and then years later or sometimes months later, they're actually found to have metastatic disease. So they go on later on to develop distant recurrence.

And very small number of women are actually diagnosed with de novo metastatic breast cancer, and that's when they just come to attention by doing a biopsy and they've never ever had a breast cancer diagnosis before. But when it does get diagnosed at initial presentation, it's actually metastatic.

So very briefly, median survival. These are just statistics, not my patients. Not all will follow these statistics. We're not the statistics. Patients do not follow what's in the books. But generally, five-year survival is about 25%, so still in 2023, it's considered to be a chronic disease. So, for women with stage four breast cancer, systemic therapy is the mainstay of treatment. And so these include hormonal therapy, chemotherapy, targeted drugs, which we're going to talk about, as well as immunotherapy, or a combination of these. So surgery and radiation generally does not have a big role in metastatic disease, although in certain situations we do use them.

Okay, so what do we try to do when we treat breast cancer? What are we trying to accomplish in treating metastatic breast cancer? Well, the main goal is really prolonging survival, but we have to put that in the context of the quality of life of the patient, which is extremely important. So, when we sit down and decide and talk with the patient in regards to their treatment options for their newly diagnosed metastatic breast cancer, we want to take into account their quality of

life, meaning, by reducing their cancer-related symptoms, what can we do to reduce the cancer-related symptoms? What can we do to minimize the toxicity from therapy and delay the chemotherapy as far out as possible and increase the progression-free survival?

So the good news about breast cancer, or metastatic breast cancer, is that for a long time we've had lots and lots of options to choose from. So it's not like sometimes melanoma or lung cancer that you had few options to deal with or pancreatic cancer. But in breast cancer, we have a lot of options to choose from. But one of the important factors that we take into consideration, again, is the quality of life of the patient. So, when we are at a point where we're sitting down and we need to change therapy and choose between two drugs that are equally effective, we will think about which one will actually fit the patient's life best. So, again, quality of life is very important.

The other good news about metastatic breast cancer is that the survival has dramatically improved. And we'll look in the next slide, but the median survival in the 1990s was only 13 months. And in 2010 and beyond, it's changed to 33 months. So you can see here, this may not be very legible, but in the 1990s, we only were dealing with almost a year or two of survival, but after 2010, that survival has dramatically increased. And when we look at this gain in survival, we can see that it's most notable in HER2 positive disease, but so is the other kinds, like HR positive, hormone receptor positive, or triple negative. But we have had least success with triple negative and most success with HER2 positive in terms of survival. And that's really related to the profound effective therapies that we have nowadays in 2023 for HER2 positive disease.

So, this is just a brief overview of what the different kinds of breast cancer are. So I'm going to be talking about the differences in the tumor types, and I wanted you to know that we refer to some cancers as ER positive, so estrogen receptor positive, Luminal A, Luminal B, could be ER positive, HER2 negative, these are just simply receptors that are present on the surface of the cancer cell. And if they're amplified or if they are existent, then we call it positive. And if they're not there, we call them negative. And so, you can imagine a variety of options can be in the tumor. So a tumor can be ERP or positive, HER2 negative, or all three negative, or all three positive, et cetera. And this actually has an impact on the decision to how to treat metastatic breast cancer.

So, we'll talk about some of the prognostic factors. So there are a number of factors that impact prognosis, and we actually take into account all of these factors to decide on the therapy options for our patients. So for example, if somebody has been diagnosed with breast cancer 10 years ago and now all of a sudden they're diagnosed with metastatic disease, that's a more favorable prognosis. So if the interval, relapse-free interval is over two years, that's still favorable. There's still a good chance that those patients can go into a long remission again with the new therapies, even though they have metastatic disease. Whereas somebody who has a diagnosis of breast cancer early stage, or

what we think is early stage, and then two months later we find a bone metastasis or something that would be less favorable.

Also, the subtypes. So still in 2023, we think that if our patients are estrogen receptor positive breast cancer, they have a better prognosis than if it's an ER negative or if it's triple negative. Now, HER2 used to be a worse prognosis. I remember when I was at City of Hope in 2001, starting my fellowship, back then the HER2 receptor detection had just come out and we were considering those untreated HER2 positive patients, even worse prognosis than triple negative. But that's not the case anymore. So in the last few years, we've had many powerful therapies against HER2 disease, and therefore HER2 positive cancer is now considered a better prognosis. Also, prior adjuvant therapy or metastatic disease will also make a difference. So if patients have been heavily treated in the past, then that brings about a worse prognosis.

So these are some of the sites of the disease that, for example, we know bone-only disease will have a really good prognosis. I've had patients with bone metastases that have been on pills, therapy for five, seven years and they're still ongoing and really they have a good quality of life and their survival has increased, whereas when we have other sites such as lymphogenic spread in the lungs, which is the spread of the cancer into the lymphatics inside the lungs, or leptomeningeal disease, which is a spread of the tumor inside the brain or the cerebrospinal fluid, then that brings about a worse prognosis.

So, I put this slide to show you that we absolutely individualize treatments to not just the patient's characteristic but the tumor characteristic. So when we are approaching management of these patients, we're taking into account all of these factors. What are the characteristics of the tumor? What are the characteristics of the patient? And have they had any prior therapy? What is their status of germline mutation? Do they have any symptoms? What are their preferences? And we'll take all of that into consideration before we actually formulate a plan of care.

This is a kind of cartoon picture, a very simplified picture of how we treat metastatic breast cancer according to the hormonal receptor status. So on the left in the green, we have some of the options for hormone receptor positive HER2 negative, in the middle it's HER2 positive, and then on the right side we have the triple negative, which most of the time we use chemotherapy. But this is actually not a very old slide, but it's already outdated, telling you how we advance in breast therapy and breast cancer treatments so quickly, like every month there might be a new drug coming up.

So, I wanted to make sure that you all know, when we come across finding somebody who has metastatic breast cancer on the imaging, we tend to want to biopsy all the time because it's important to establish the diagnosis, making sure that we confirm the status of the receptors, because a lot of times, that original breast cancer may have a different hormonal receptor status than the metastatic in actually about 5% to 30% of the time. And that makes a difference because if

we just go based on the original breast diagnosis and if the original breast cancer was ER positive and we treat the metastatic as such and don't test it, then we could be potentially taking away that opportunity from the patient to have a better treatment. So, we always want a biopsy, number one, to make sure that it's not anything else. Maybe occasionally we come across situations where you biopsy a node in the lung and it happens to be sarcoidosis, which is not malignant, or it could be a second primary. So sometimes patients develop two primary cancers, so you want to make sure what we're treating is correct.

So, if the receptors are not the same, then what do we do? Well, the American Society of Clinical Oncology says that you go based on the new diagnosis, based on the biopsy of the metastatic area to make decisions about the treatment. We're also using molecular profiling of the tumor more and more in the last four, five years, there's been all kinds of new generation sequencing. These are DNA sequencing, genetic sequencing of the tumor itself that guides us to make treatment decisions because they might qualify the patient for a new targeted therapy, for a pill therapy, or sometimes clinical trials. And if the tissue diagnosis is not available, because sometimes you may have a little tissue to deal with, then a liquid biopsy is encouraged. And we use this nowadays quite a bit to make decisions on treatment options.

So, I want to focus a little bit in the next few slides on how we treat HER2 positive disease, because HER2 positive untreated used to be very aggressive, but now we have a lot of powerful treatment options for it. There are generally three categories of therapy options for HER2 positive metastatic breast cancer. These include the monoclonal antibodies, which many of us may have heard of, Trastuzumab, or Herceptin, Pertuzumab, or Perjeta. And then there are antibody-drug conjugates. These are novel agents that are a combination of chemotherapy and an antibody. And we're going to see a picture of that, a slide on this, and I'll show you how they actually work. There's two main drugs that we use, T-DM1 and T-DXd. We use them for metastatic breast cancer. And then there is the tyrosine kinase inhibitors, which is three of them; Lapatinib, Neratinib, and Tucatinib.

Here they are. We have the monoclonal antibodies, they work outside of the cell, Trastuzumab, Pertuzumab, and they block this HER2 receptor. And then we have those antibody-drug conjugates, which actually works in a way that the antibody is linked to a drug, which is usually chemotherapy, and then it actually brings it into the cell and then releases the chemotherapy into the cell and that chemotherapy will kill the cancer cell basically. And then there's these tyrosine kinase inhibitors referred to as the TKI, which are inhibitors of certain proteins, and that's how they essentially kill the cancer cells.

So, there were two pivotal phase three trials in 2001 and 2005 that changed the treatment for breast cancer and for HER2 positive breast cancer forever and ever. And these two were the Dennis Slamon in 2001 and Marty JCO in 2005. They essentially added Trastuzumab to the original chemotherapy for patients and noted an overall survival benefit, which was really unheard of for a drug in

breast cancer. And that introduced, that was the initial introduction of the Herceptin. As soon as these trials came out, people started using HER2. In fact, I remember in 2001 when this study was coming out, I was at City of Hope and my attending and I were seeing a patient together and a lady walked in with newly diagnosed breast cancer, HER2 positive, but at the time, it was still not FDA approved and she was requesting for Herceptin, but thankfully we were able to get it to her within the next few months. But it was a battle to try to get that for her because it was just at the beginning of the time when Herceptin was being recognized.

I'm going to go through some of these slides relatively quickly. This was an important trial, Cleopatra trial. Years later, after Herceptin came out, that tested a drug or actually added the Taxotere chemotherapy to the monoclonal antibody Herceptin. And then they said, "Okay, why don't we just add one more monoclonal antibody to this regimen? And they did. And so this is the bottom one, the green one. There were two monoclonal antibodies, Trastuzumab and Pertuzumab, added to the chemotherapy. And this is a survival curve showing that the top line, which has a better survival with adding Trastuzumab and Pertuzumab, by at least, so the overall survival was 57 months versus 40 months, so an improved 16 months overall survival. And that added the second monoclonal antibody, Perjeta, to the drug armamentarium that we had for HER2 positive breast cancer.

T-DMI came next. This was, again, an antibody-drug conjugate that actually started being used as a second line regimen. Again, because of the overall survival benefit. I'm showing you these slides because I want you to have a feeling of how the oncologist or how the oncology field decides what to give. So, based on these clinical trials, when we see survival benefits, we actually take that into our practice and add that. And usually, these trials are presented in the international societies such as American Society of Clinical Oncology, and everything that comes out of that is considered godsend for us. And so we start using that in our practices. So T-DM1, or the other name is Kadcyla, became the second-line therapy for HER2 positive disease. This is how it worked, the antibody-drug conjugate, this was using the antibody, which was an anti-HER2 antibody. And then they linked a chemotherapy drug, such as Topoisomerase, to that, and they made this drug called T-DXd. And so after the T-DMI, then T-DXd came out and was introduced to the market, and this one replaced T-DMI after this Destiny trial showed that it had, again, a better survival curve.

So, then the T-DXd, which many of you may know by the name Enhertu drug, became the second-line best treatment for HER2 positive disease. Yet another category of tyrosine kinase inhibitor drug came out. I'm showing you this one, Tucatinib, because this drug was unknowingly, they didn't know, they added patients to this trial who had brain tumors from metastatic breast cancer. And these patients were randomized to two groups. Half of them got Tucatinib, Trastuzumab, and Capecitabine, which is another chemotherapy, and the other half got placebo Trastuzumab and Capecitabine. And so, the patients who did receive Tucatinib regimen, they actually had a much better survival.

But then when they looked at this category, they noted that many of those, or some of those patients, had actually entered the trial with the diagnosis of brain cancer. And this is unheard of. We generally don't get patients with metastatic breast cancer to the brain to participate in the clinical trials. But these were patients that had minimal disease or they had stable disease, they had already been treated with radiation. And what they noted is that they all responded to the Tucatinib, even those patients who had a brain tumor. And so Tucatinib became one of the favorite options for HER2 positive disease with metastases to brain. So HER2 positive has this propensity to want to go to the brain, and we don't have too many options that actually travel the blood-brain barrier to treat the brain cancer or the breast cancer that's traveled to the brain. And Tucatinib was one of the drugs that were showing that efficacy.

I know that these slides are being saved for later. So for those of you who really want to know what to do first line, second line, third line, this is a format that we generally use for our HER2 positive disease, and it's all in here. We use the first line for Trastuzumab, Pertuzumab, and we try to stay with this category. When you get to beyond the third line, you have many other options that you can consider. So as you can see, there are many, many options of therapy for metastatic breast cancer HER2 positive.

Now we're going to switch gears to hormone receptor positive HER2 negative breast cancer. And here we use a lot of pills. Endocrine therapy. Again, this is a relatively simplified and cartoon picture of how we manage hormone receptor positive metastatic breast cancer. We used to categorize it into two simple categories. One, we would say, "Okay, is there any visceral metastases? Is there liver metastases? Is the cancer in the liver or other soft tissue organs?" And if yes, we would say, "Okay, well let's just go straight to chemotherapy." And if the answer was no, if we had less bulk of the disease or if it was just in the bone, then we would consider endocrine therapy. And by that, I mean Tamoxifen, the aromatase inhibitors that we use as the endocrine or anti-estrogen therapy.

But this actually has changed quite a bit in the last few years when another category of pills have come out by the name CDK4 inhibitors, and we're going to take a look at that. So, there were three main trials that came out with three different pills. All these three have very similar mechanisms of action, Palbociclib, Ribociclib, Abemaciclib. Based on three clinical trials, all three showed that when these medications are added to the Tamoxifen or aromatase inhibitor, meaning the endocrine therapy, they actually increase the progression free survival. So the time that the patient had and surviving without their disease coming back was dramatically increased. Look at this 24 months versus 14 months for Palpo, and 25 months versus 16 for Ribo, and so on.

And then when we look at the overall survival, they noted that these two medications, Ribociclib and Abemaciclib, actually had increased or improved overall survival. So, this makes us, as oncologists, to want to give these two medications when we have metastatic hormone receptor positive HER2 negative disease, rather than this one because these two show that, hey, the overall

survival is even better rather than just the progression-free survival, and that makes a difference. So, our drug of choice in 2023 for a woman with metastatic breast cancer hormone receptor positive, despite how much disease they have in the body, whether they have bulky disease, a lot of bony disease, some liver problems, some lung metastases, et cetera, we actually choose these pills, these medications that are pills rather than chemotherapy. And as we will see in a couple of slides I think from now, they showed that those patients actually do better than when they are given chemotherapy. So, these are very novel changes and improvements in the breast cancer therapy these days.

So obviously, these drugs, they're pills, but they're not without side effects. Some of them will actually cause neutropenia, so they can lower the immune system, but they've noted that those episodes are not really associated with increased infection, it's just something that would need monitoring by your oncologist, and many of them are quite tolerable. My experience with my patients have been, they've had an amazing tolerability to these medications. Of course, they have some differences in their toxicity. For example, Ribociclib, which is our favorite drug and our first choice, can sometimes prolong the QT interval. And so a patient would need to have some periodic EKG to monitor for that.

Here it is. So this category called CDK4 inhibitors, they're typically used in the first-line setting along with the endocrine therapy or anti-estrogen therapy. We use them in estrogen receptor positive disease. And a recent study showed that they actually have superiority compared to chemotherapy, even if we're dealing with significant burden of the disease. And they're equally as effective in older individuals.

Okay. So, next we're going to go beyond endocrine therapy, beyond the first line. What if the patient who has metastatic cancer with estrogen receptor positive, they failed their Tamoxifen or the anti-CDK4 inhibitor, what do we do next? Well, there are molecular mutations that can make a patient eligible for other drugs. One of them is this PIKC3A mutation in women. And this mutation can be ascertained or assessed by checking the tumor. So, all it takes is sequencing the gene of the tumor and finding this mutation. And if this mutation is present, then they will be eligible for a drug called Alpelisib.

This is, again, a summary of the endocrine therapy that we use for estrogen receptor positive metastatic breast cancer.

Next we go to chemotherapy. There are certain cases where we have to use chemo upfront rather than endocrine therapy or pills because of certain situations. Again, it has to do with the characteristics of the tumor. For example, in triple negative, when the estrogen, progesterone, and HER2 are all negative, those patients generally do not respond to any anti-hormonal drugs such as Tamoxifen or Arimidex or Letrozole, and they generally get chemotherapy upfront. So, here the goal is to continue with that chemotherapy regimen as long as there is no progression or as long as we don't have unacceptable

toxicities. Here, the goal is to offer palliation. And there are, again, many options for chemotherapy. For HER2 positive disease, we try to add the anti-HER2 therapy because it increases the effectiveness of the regimen. And if they're ER positive, then if there is a lot of bulky disease in the liver and the patient's completely symptomatic, sometimes we choose chemotherapy at least upfront for a little while, and then we switch them to pills.

This is a very famous medication now, Trodelvy, or the other name for it is Sacituzumab govitecan, which we use in second-line therapy for metastatic triple negative breast cancer. And now has become, just in the last few months, has become a second-line favorite for triple negative breast cancer. So what do we do in triple negative breast cancer? The role of immunotherapy has now been more and more into the picture. We used to just use chemotherapy, but now we actually have the option of adding immunotherapy to the regimen, and these are drugs that will literally make the immune system unblinded so that they can get the cancer and capture the cancer and kill it. And so these immunotherapy drugs are very well known, they're drugs such as Pembrolizumab, Opdivo, I'm sure you've heard the commercials on TV. And so that's for patients that have this particular receptor called PD-L1. And if the PD-L1 is positive or more than 10%, we choose to add immunotherapy to the chemotherapy for triple negative disease. Okay?

Melissa Rosen: Doctor, I just want to hop in here for a second. We have so many questions that I want to get answered, so I just want to... Can we...

Dr. Bahareh Bah...: Sure, certainly.

Melissa Rosen: Thank you.

Dr. Bahareh Bah...: Of course, of course. So how much time do I have?

Melissa Rosen: So I'd love to be able to offer 10 minutes worth of questions, so just a couple more minutes.

Dr. Bahareh Bah...: That's perfect.

Melissa Rosen: Thank you so much.

Dr. Bahareh Bah...: This is a summary, goals of therapy in decision-making for metastatic breast cancer. We talked about the HER2 positive versus HER2 negative, and so the chemotherapy options, we prefer single agent rather than combination. And the last thing I want to tell you is that for BRC1 and 2, these are the hereditary genetic mutations, we actually offer pill drugs called PARP inhibitors.

Molecular profiling is very important in treatment decision-making and bone-targeted agents are also available to target the cancer in the bone. So, for metastatic breast cancer, we always encourage early diagnosis and effective

treatment of all types of cancer are crucial when we actually find them early on rather than when we have a lot more disease.

And lastly, I wanted to tell you, there's always hope beyond what you see. It's possible not just to survive, but to thrive and to live a healthy, wonderful life. Life is 10% what happens to us, 90% how we react to it. I love this slide. I was looking for a slide to share this journey with you. I think it's a spiritual journey, but please keep in mind balance and just peace of mind is important. Stress management techniques, get help from families, social support, your doctors, and just try to see it as a spiritual journey, just like Ilene said. Thank you very much.

Melissa Rosen: Thank you. Thank you so much. Thank you. You've given us so much information about the hope that is out there, and I actually think the first question I want to ask dovetails beautifully with how you ended it. You just said, we want to be sure that we catch metastatic disease as early as possible, and so many of us who have had breast cancer are told there's no routine mammograms or blood tests or anything after. So, if we're not routinely tested in those ways, how do we monitor? How does one diagnose metastatic disease after either months or years after having dealt with stage zero through three?

Dr. Bahareh Bah...: Sure. Very good question. So there are several factors that actually bring an oncologist red flags to look for metastatic disease. One of them are tumor markers. For stage two and three breast cancer, not always for stage one because we use NCCN guidelines, which are National Comprehensive Cancer Network guidelines and for stage two and three we can do tumor markers, which are a part of the routine follow-ups with the oncologist. One of the ways that we notice that cancer might be back is that the tumor markers become abnormal after being normal for a long time.

The other way is by new symptoms. When the patients present to their clinic appointments, they may complain of bone pain or I've been having headaches recently. I tell all my patients when they're in survivorship to look out for symptoms and signs such as headache or bone pain, back pain, and something that is persistent for three weeks or beyond would definitely have to be evaluated. And then at that point, you can actually focus your evaluation with an appropriate imaging or blood test. So for example, if the patient has a headache, you get an MRI of the brain. If they have multiple symptoms, we get a PET CT, which is kind of like the total body imaging, or if they have bone pain, I generally in my practice order a lot of bone scans. It's quite safe. And-

Melissa Rosen: Thank you. You mentioned first tumor markers. That's done through routine blood work?

Dr. Bahareh Bah...: Correct.

Melissa Rosen: Okay, great. Somebody asked, do pre existing conditions, other than cancer, make metastases more likely in certain areas? In other words, if somebody had liver disease, is it more likely they would, if they were going to have a metastasis, it would go to the liver rather than bones or brain or lung?

Dr. Bahareh Bah...: Very good question, and we don't have any proof of that. So the general answer is no, but we know that, as a routine, any part of our body that has experienced chronic inflammation over time, it would be prone to be unhealthy and I should say, less healthy. And so, for that reason, if that organ becomes weaker, it's a possibility of that. But scientifically, we don't have any proof that that's the case.

Melissa Rosen: Okay. Thank you for that. A couple of people ask, just for clarification, if somebody is initially diagnosed, not de novo, just diagnosed with breast cancer, but there is cancer found in lymph nodes, does that mean they have stage four and it is a de novo diagnosis or unrelated?

Dr. Bahareh Bah...: So, no. So there's locally advanced breast cancer and then there's metastatic breast cancer. When we say metastatic breast cancer, it has to be to other than the regional lymph nodes. So if a person is diagnosed with stage two or three breast cancer where the tumor originally in the breast traveled to the unilateral, the same side armpit lymph nodes, that's still not metastatic. But let's say a patient has a right-sided breast tumor and then the left axillary lymph nodes are involved, that's metastatic. Does that make sense?

Melissa Rosen: Yeah, it makes sense.

Dr. Bahareh Bah...: It's kind of a hit and miss, but generally distant metastatic disease, distant travel of the tumor is considered metastatic disease. So we consider metastases when it travels to the lung, bone, liver, brain, and also pleural effusion. So, the fluid that accumulates in the bottom of the lung, even though it's not inside the parenchyma of the lung, is still considered metastatic disease.

Melissa Rosen: Okay. Can you explain why it is that a first line eventually stops working and a second-line treatment? What stops working? What makes it that these treatments that were effective no longer are effective? Is it because the cancer has changed? Is it adapted? What is it?

Dr. Bahareh Bah...: So, many factors. Depends on the biology of the tumor and also the effectiveness of the efficacy of the treatment that we're offering. Many times, for example, if the tumor is ER positive and we're giving the treatment for ER negative, unknowingly, because we don't have the most accurate information, that's one of the reasons for lack of response. The second lack of response is when the tumor actually mutates, so the cells in the tumor will become resistant. And there are many mechanisms of resistance that there's not enough time for me to go over, but essentially the tumor is smart enough that it develops pathways to resist the drug, is the simplified way of saying it.

Melissa Rosen: Okay. Related to that, somebody asked, and I don't even know if I took notes on it, but I remember somebody asked, is there any chance or likelihood that someone with stage four can go a significant amount of time, and what does significant amount of time look like, between treatments? Or are they always on some form of treatment?

Dr. Bahareh Bah...: So the answer is yes. Generally, patients that are estrogen receptor positive, rather than negative, can have a long-term remission in between the therapies. I've had patients where I remember in the first five years of my practice as an oncologist, I had a patient who came from out of state and the cancer was in the bone, metastatic breast cancer in the bone, and her forehead bone was literally protruded up to here. And at the time, we had nothing but the aromatase inhibitors, the anti-estrogen, we didn't have any of these new drugs. That lady went on 10 more years with that just one pill and responded, and she's still alive. But the duration of the response to that drug was 10 years.

So, again, bone-only disease has a better response or longer response. Triple negative will have a shorter response to the treatments, but yes, the correct answer is yes. There's a possibility that you can go very long in between the treatments. Again, I have a patient who was presented to me from another physician, initially had very early stage breast cancer, and then several years later, while on Tamoxifen, they noted that her liver enzymes were elevated. So then we started doing tumor markers, and before you know it, she did have a lesion in the liver. One lesion in the liver, nowhere else was the disease, not even in the breast, but it was breast cancer. So we resected it, and that was 10 years ago. That's still metastatic breast cancer, but with a resection. And so she's only on a pill as of now, 10 years later.

So the chances are that you will likely be on some form of therapy for a long, long time. That scenario is more likely to be the case than being off therapy for a long, long time, but we can withdraw therapies as we go along if we can get by with minimum. That's what we do.

Melissa Rosen: Okay. Being very aware of the time. I know that there were other questions. I tried to ask the more general questions. I'm going to encourage those who had more specific questions about a specific treatment or a specific type of breast cancer, if you are part of the Embrace, which means if you are living with stage four breast cancer, to stay for a more intimate conversation with Dr. Bahadini. But first, I want to thank you so much, doctor, for sharing your unique expertise with us this evening. And Ilene, thank you so much for sharing your story. I learned so much today and I hope you did as well.

And if you want to learn more about MBC, metastatic breast cancer, and Sharsheret's resources for caregivers, those directly impacted, and even healthcare professionals, check out our newly updated website page on metastatic cancer. The link is in the chat right there. We have lots of new resources, including an updated version of our booklet, From the Spiritual to the Practical, which is actually geared specifically toward caregivers of those facing

metastatic disease. And another new piece that provides even more myth-busting information. Both of those will be available to download from our website or to order hard copies in early January.

Before I share my final thoughts, those who are impacted, again, by metastatic breast cancer and who are planning on staying on for our conversation with Dr. Bahadini and with Bonnie, please stay where you are and as the main part of the webinar concludes, Bonnie will begin the breakout session. But I want to take a moment to thank once more our generous sponsors, including Gilead Oncology and the CDC. Please take a moment to fill out the brief evaluation survey on today's program. The link is in the box now and will be entered into the chat box again after the breakout session.

Next week, you will receive a follow-up email with the link to the recording, transcript, and access to some of the additional resources I mentioned, so please be on the lookout. And finally, please remember that Sharsheret is here for you and your loved ones. Sharsheret provides emotional support, mental health counseling, and other programs designed to help you navigate your cancer experience. All are free and completely confidential. You can reach us at the email address in the chat box below. Simply clinicalstaff@sharsheret.org. Thank you for joining us and have a wonderful evening. Those of you who are staying, please hang tight, Bonnie will begin in just a minute. Everyone else, good night.

Bonnie Beckoff: Thank you Melissa, very much appreciate it. Ilene, thank you so much for sharing your story, and Dr...