

Yale CANCER CENTER *answers*

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Hosts

Anees Chagpar MD

Associate Professor of
Surgical Oncology

Francine Foss MD

Professor of Hematology

Steven Gore MD

Director of
Hematological
Malignancies

Therapies for Advanced Breast Cancer

Guest Expert: Maysa Abu-Khalaf, MBBS, MD

*Associate Professor of Medicine, and of
Obstetrics, Gynecology, and Reproductive
Sciences, Yale School of Medicine*

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Welcome to Yale Cancer Center Answers with your hosts doctors Francine Foss, Anees Chagpar and Steven Gore. Dr. Foss is a Professor of Medicine in the Section of Medical Oncology at Yale Cancer Center. Dr. Chagpar is Associate Professor of Surgical Oncology and Director of the Breast Center at Smilow Cancer Hospital and Dr. Gore is Director of Hematological Malignancies at Smilow. Yale Cancer Center Answers features weekly conversations about the research, diagnosis and treatment of cancer and if you would like to join the conversation, you can submit questions and comments to canceranswers@yale.edu or you can leave a voicemail message at 888-234-4YCC. This week you will hear a conversation about therapies for advanced breast cancer with Dr. Maysa Abu-Khalaf. Dr. Abu-Khalaf is Associate Professor of Medicine and of Obstetrics, Gynecology, and Reproductive Sciences at Yale School of Medicine. Here is Dr. Anees Chagpar.

Chagpar Maysa, why don't you start by telling us a little bit about what we mean when we say advanced or metastatic breast cancer? What exactly is that?

Abu-Khalaf Breast cancer cells, when they start growing, they start growing in the ducts and lobules within the breast and as a tumor grows it then spreads to the lymph nodes and through the bloodstream to other parts of the body. Once the cancer travels and grows in distant organs like the liver, lung or brain, that is when we will call it advanced or metastatic disease, we is also called stage IV cancer.

Chagpar At that point does that mean you are going to die or is there still hope for these patients?

Abu-Khalaf There are many, many treatments for patients with advanced breast cancer. It has changed significantly over even the past 5 to 10 years and patients can live many years now, unfortunately we cannot predict upfront which of these tumors are going to respond or not so we have to wait and give appropriate treatment and monitor the patients and see how the cancer responds. It is different than the early stage breast cancers where we can't cure these cancers with a very rare exception, but in general it is life-long treatment. I tell my patients to think about this as a chronic disease, you are going to go on treatment like you would for any other disease such as high blood pressure or diabetes and we just continue to follow them closely and watch how the tumor responds and there are many options, so if one does not work we will always try to find another one that does.

Gore Maysa, could you clarify for our audience, I know a lot of my patients and certainly my lay friends seem to think that if they had breast cancer and a tumor comes up in their liver, they now have liver cancer, can you explain that?

Abu-Khalaf It is a bit confusing, we typically will call it metastatic or advanced breast cancer. We name it based on where it starts, so a liver cancer is a cancer that starts in the liver, but metastatic breast cancer or stage IV cancer that has gone to the liver is a different disease. So you treat it as a breast cancer with treatments that work for breast cancer.

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Gore And the same would be true in the bone or the brain or anywhere else, is that right?

Abu-Khalaf Correct.

Chagpar Tell us a little bit more about how you work up these patients, what are the treatments? Because a lot of people with stage IV do think about, am I going to die? And that there are treatments that help people live a long time is really wonderful news. Tell us a little bit more about those treatments and where that is going and is there hope on the horizon?

Abu-Khalaf Yes, definitely. There are a lot of new treatments also being investigated so we have a lot of treatments and we are looking forward to more novel treatments in the next few years. When the patient comes in with early stage breast cancer, typically if they have a larger tumor, a tumor that is larger than 5 cm or multiple lymph nodes, we tend to stage them. We will get a CAT scan and a bone scan or a PET scan, those are x-rays of the body to look at any possible spread of the cancer when they present. The majority of the patients do not have metastatic disease when they present at an early stage. For stages I and II, the recommendation is not to get these scans unless the patients have symptoms. If a patient presents with a lump and while they are being diagnosed they get a biopsy and see a medical oncologist and suddenly they have new onset or worsening back pain, headaches that they have never had before, blurring of vision, then we start looking for cancer. Otherwise, it is really for patients who have the larger tumors and multiple lymph nodes. Once you find something suspicious on a CAT scan or bone scan or PET scan, you need to confirm that it is truly metastatic disease and we do that by getting a biopsy. So tissue biopsies can be done with the help of a surgeon or radiologist by targeting that suspicious area and collecting tissue. Once it is done, it goes to a pathologist or a pathologist looks it over under the microscope and confirms that it looks like it is breast cancer cells and then we need to try to figure out what other features it has, so when we treat breast cancers, there are three major proteins we look at. There is the estrogen protein and then there is a progesterone protein and those are what we call hormone proteins or hormone receptors and they are expressed in about 80% of breast cancers and it is important because these cancers tend to behave a little bit differently, but we also have treatments that target these proteins. There is a third protein called the HER2 protein and that is expressed in about 25% of breast cancers. In the past, we used to feel that these were more aggressive cancers and tend to spread more and are more likely to present with metastatic disease. Right now, when we find these cancers in the earlier stage, we have highly effective treatments and less and less patients have disease recurrence or progression after they are initially diagnosed. Once we determine whether these proteins are present or not, we can tailor treatments. So, an estrogen receptor positive tumor tends to be a hormone driven tumor and that means it grows and feeds on the hormones in one's body. Estrogen and progesterone are female hormones and even when postmenopausal we still have enough to cause trouble. So, there are different ways of blocking the hormones in the body from getting the breast cancer cells. There is a drug, for instance, called tamoxifen that works directly at the level of these estrogen and progesterone proteins and blocks the hormones in the body from being able to get to these cancers. There are

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classifications, they are called aromatase inhibitors and they reduce the production of estrogen. So, the end goal is really to have less estrogen or less hormones get to these cells so that we can slow down the growth. When you have a HER2 protein, it is a little bit different, and it is signals that feed these proteins, which leads to them growing faster and spreading. In the past, the only treatment we had was chemotherapy, but now we have multiple agents that target this HER2 protein and we call it a targeted therapy, meaning the drugs target specific molecules or proteins or pathways in the breast cancer that usually lead to growth and division of these cancer cells, by targeting these proteins, you slow it down. Chemotherapy, for instance, kills cells, you give it intravenously or by mouth and it travels throughout different parts of the body and kills the cancer cells but sometimes it does affect healthy growing cells. So, we tend to have more side effects such as hair loss, nausea, vomiting and mouth sores because the normal cells in the body are affected. The targeted proteins usually affect the cells that have that molecule. So, when you treat patients with a drug such as trastuzumab, it is also known as Herceptin, it is a drug that targets the HER2 protein and by doing that it slows down the tumor growth. It usually works better with chemotherapy and for the most part we treat patients with chemotherapy and trastuzumab. It is used in the early stage breast cancers for about a year and does wonders and it has saved many lives, so many women who had HER2 positive tumors now live longer and are cured of their cancer because of this drug and in the metastatic setting, it has also slowed down the tumor growth where patients live longer without having to switch treatments and without their tumors progressing. There is another drug that was also approved recently in combination with Herceptin chemotherapy called Perjeta or pertuzumab and it binds the HER2 protein at another site and it prevents its interaction with other members of the HER family, so other proteins, and by giving chemotherapy such as Taxotere or Taxol, or we also call them docetaxel and paclitaxel, and giving the Herceptin and Perjeta, when you give them altogether they work a lot better than if you give chemotherapy alone or chemotherapy with Herceptin and this regimen is also used in the early stage cancers and you see cancers melt away in the early stage and you see a good response in the metastatic setting as well.

Gore You got me a little bit confused, let's say I am a patient with early stage breast cancer and it sounds like depending on my characteristics I might have gotten chemotherapy to prevent recurrence and now it is some time later and I have metastatic disease and I have to go through this targeted thing and chemotherapy, does everyone have to get chemotherapy with recurrence?

Abu-Khalaf Yes and no. At some point, yes, and there are different ways, the American Society of Clinical Oncology recommends that we consider chemotherapy, the Herceptin and Perjeta, as first line treatment for metastatic breast cancer and we can give the chemotherapy for about six cycles or so and if we find that patient's respond and are doing well, you can pull back from the chemotherapy and continue the other antibodies, because you will have less side effects and you can continue doing that as long as they are responding and there is no disease progression. When the patients' progress, the metastatic disease either grows or you start seeing other spots in the body, you switch

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to a second line treatment. There is a drug that is a really good drug called Kadcylla or T-DM1. Basically, it is an antibody conjugate drug, so it's Herceptin combined to chemotherapy and the nice thing about this drug is that instead of giving chemotherapy through the vein and it goes everywhere throughout the body, when you combine the chemotherapy to Herceptin, it goes where Herceptin would go and that is towards the breast cancer that expresses HER2.

Gore Like a smart bomb.

Abu-Khalaf Yes, and that is actually an area of interest in breast cancer now and in many cancers, obviously, trying to direct treatment to where the cancer is and less to other parts of the body. So that would be your second line treatment and you continue on that so long as the patient is responding and so long as the tumor is responding and there is no significant toxicity, because we always try a balance between trying to target the tumor and how the patients feel. When we talk to patients about the goals of care and metastatic breast cancer, we want to try to control the cancer, we would like them to live as long as possible and also maintain quality of life, because we can help with a lot of treatments all at once, but the patients will struggle with that and that is why it is always a fine balance. We typically try to do one chemotherapy at a time if we are going to do that and combine it with the targeted therapy rather than multiple chemotherapies like we do for an early stage breast cancer.

Gore Do people ever switch from one of these hormone responsive breast cancers to one of these HER like breast cancers, how does that work, do we have to biopsy them with each recurrence?

Abu-Khalaf Typically what we do if a patient has an estrogen receptor positive tumor, you start with the hormone blocking agents and you continue switching from one to the other based on responses and ultimately you switch to chemotherapy. There are rare instances where a cancer can be HER2 negative or ER negative and switch to being positive or vice versa. Therefore, if it has been a long time between the first biopsy, we consider re-biopsying especially after recurrence.

Gore We will pick up on that after the break. Right now we are going to take a short break for a medical minute.

Medical Minute

The American Cancer Society estimates that more than 60,000 Americans will be diagnosed with head and neck cancer in 2014. Although the percentage of oral and head and neck cancer patients in the United States is only about 5% of all diagnosed cancers, there are challenging side effects associated with these types of cancers and their treatment. Clinical trials are currently underway at federally designated comprehensive cancer centers such as Yale Cancer Center and at Smilow Cancer Hospital at Yale-New Haven to test innovative new treatments and in many cases less radical surgeries are able to preserve nerves, arteries, and muscles in the neck enabling patients to move, speak, breathe, and eat normally after surgery. This has been a medical minute, brought

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to you as a public service by Yale Cancer Center and Smilow Cancer Hospital at Yale-New Haven. More information is available at yalecancercenter.org. You are listening to the WNPR Connecticut Public Media Source for news and ideas.

Gore Maysa, before the break you were telling us that sometimes the breast cancer cells can change over time and sometimes we need to re-biopsy to further characterize them and pick the right therapy at that time. Is that right?

Abu-Khalaf Yes, and I think that it is important to know that if somebody presents with an early stage cancer and then let us say many years later there is a recurrence, or we find metastatic disease, it is very important to make sure that the receptors are the same because it affects treatment and about 10% to 20% of the time it has been reported that there can be a discrepancy. You can have a hormone receptor positive tumor that becomes hormone receptor negative, and therefore, the hormone blocking agents will not work as well. So that is typically what we do. We confirm the recurrence and in that tissue we will repeat the receptors as well.

Gore We hear a lot about personalized medicine and studying the DNA of the cancer cells to choose therapies. Does that have any role in this advanced breast cancer field?

Abu-Khalaf I think in general in breast cancer, we have been looking at personalized medicine because everything we do, looking at the estrogen receptor, the HER2, this is all personalized towards that. In addition to that, there are now more novel therapies that are being developed and what we find is that similar to our estrogen receptor and HER2 receptor, we need to find targets where you can select patients upfront with tumors that are likely to respond, so rather than giving everybody the same treatments and trying to figure out if it works or not, we are trying to select out tumors upfront that have a protein or gene that is abnormal, that is more likely to make this tumor respond. So a lot of the research is in that area and we have clinical trials evaluating novel treatments that are targeting specific proteins and genes. So it is very important that the patients know upfront that we collect the tissue, sometimes we have to get another biopsy, something more recent to be able to look at these markers and try to select the best clinical trial treatment for them, when they are ready for a clinical trial.

Chagpar A lot of people hear the words clinical trial and they think, not me, I am no human guinea pig, go experiment on someone else, but people who participate in clinical trials tend to do better than people who do not, in part because they avail themselves of the more novel therapies that you are talking about. Can you review for our listeners what exactly a clinical trial is? How scary is it? What are the advantages and disadvantages of participating in a clinical trial and how in general do these things work?

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Abu-Khalaf A clinical trial is basically clinical research, where you treat a large number of patients, and that varies depending on what type of clinical trial, with a new drug or a combination of new drugs and you follow these patients very closely to see how well they respond and how safe the drug is, and the idea starts very early on when our scientists find in the lab that there is a target that can be targeted with novel treatments and then it moves on to what we call phase I clinical trials where we are trying to look at the best dose for this new drug and try to get more experience with it and determine how safe it is. Once we determine that it is safe and we know how to use it and the scheduled dose, it moves to a phase II clinical trial. The phase II clinical trial is basically patients who have similar tumor types, similar stages of disease, all get treated with this drug and we follow them to get more data and results on how safe and active it is. Then, ultimately, what leads to the approval of a drug and how it becomes a new standard, it has to be studied in large randomized studies, that means sometimes thousands of women get to be treated with this drug or new drug combination and it is compared to women who get treated with the standard and if it proves to be superior, safer, then that becomes a new standard of treatment. So all the drugs that we have approved right now, went through the clinical trial phase and I think sometimes patients do not understand that. They do think it is experimental and it is in some sense, but there is a lot of thought that goes into clinical trial design. There are lots of committees in every institution and nationally in the government that look at safety and make sure that these trials are designed appropriately, that patients are not exposed to excessive harm, and we as investigators and clinicians and our research team monitor these patients very closely. The advantages of going on a clinical trial, depending on where are you are in your treatment, in early stages of cancer if they are the aggressive type, sometimes the standard treatments are not enough, so we talk to our patients and say, you will probably be getting the standard treatment plus a novel drug that makes it better so you do not miss out in a sense, you are still getting the standard treatments. If they are lower risk disease, we used to treat them with chemotherapy all the time and now we think there is a test that might tell us they do not need chemotherapy, and they can do just as well with hormone therapy. We can back off, get the hormone therapy and they can be monitored. So, it really varies and for metastatic breast cancer patients it is always a good idea to find out what clinical trials there are. No matter how good the treatments are that we have, at some point, we will run out of treatments and we have patients living for years and we want them to live longer and sometimes we run out of treatment so the next stage is to think about these novel therapies. Sometimes this is even a good idea to look at them early on after you have the first couple of lines of treatments because maybe then it is a good idea to try something that looks like it might be safe and novel. The phase I studies in general enroll patients who had prior lines of treatment so they have gone through all the standard treatments and now we are trying to look at something a little bit novel because we do not have better standard options. Phase II can be first line or second line because we have had enough information on this drug or combination that we think it might be better than the standard.

Gore It seems like people are often worried that if they enroll in a clinical trial they are going to be getting a placebo or they are at risk of getting a placebo.

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Abu-Khalaf Especially in breast cancer patients, it is very rare that you just get placebo alone. I think there are placebo studies where that means that you might get the standard treatment plus a novel treatment or the standard treatment plus placebo but you are not only getting placebo. That means you are getting the treatment that you would get if you did not go on a clinical trial and I think that even when they read the consent forms and they see the word placebo, they do get concerned and that is our job to clarify that during our meeting with our patients.

Chagpar One of the things I think that is really important about clinical trials is that it is the way that you move the field forward.

Abu-Khalaf Yes.

Chagpar It is kind of giving patients today the treatments of tomorrow.

Abu-Khalaf Yes.

Chagpar When you talked a little bit about the different kinds of breast cancer and targeted therapies and so on, are there some exciting things that are on the horizon that patients might be able to get on a clinical trial for that you think have real potential to improve life expectancy for metastatic patients?

Abu-Khalaf An area of interest is immunotherapy and there have been really positive results for immunotherapy in other types of cancer such as lung cancer and melanoma and now it is being tested especially in the triple negative breast cancers.

Chagpar Tell us a little bit first about what immunotherapy is, because for a lot of people that sounds out there.

Abu-Khalaf It is basically finding ways to enhance your own immune system to work against the cancers and there are certain molecules that can suppress parts of our immune system and if you target these molecules you can enhance the immune system so it can find the cancer and a lot of patients actually like that idea. One drug, or target actually, that has been explored like I said in lung cancer and melanoma, is PD-1, Programmed death-1, sounds terrifying but it typically can suppress the immune system and by targeting this molecule you can enhance the immune system. We have several trials at Yale, they are Phase I studies, so they are in the earlier stage of development for triple negative breast cancer.

Gore What is triple negative breast cancer?

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Abu-Khalaf Triple negative cancer is the type of cancer that does not express the estrogen, progesterone, or HER2. So basically the only standard treatment that we have for that type of cancer is chemotherapy, and once you run out of your chemotherapy options, you have to look at clinical trials and sometimes early on because if the reason that these tumors grow through chemotherapy or do not respond is an active pathway or molecule, it is really a good idea to try to see if you can target that and the way to do it is most of the studies that look at targeted therapies require a tissue biopsy or you get some of the old tissue and you look at that molecule and see if it is expressed there, and if it is, we think that the tumors are more likely to respond to these novel therapies and then those are the patients who we offer treatments.

Chagpar What if you are a patient and you have a triple negative breast cancer, if you are offered a clinical trial with something that is going to enhance your immune system versus chemotherapy itself, I mean do you have to wait until you fail the chemotherapy to participate?

Gore I am sorry, the chemotherapy failed.

Abu-Khalaf Yes, the chemotherapy fails.

Gore Yeah, the patients do not fail.

Abu-Khalaf No.

Chagpar Granted, however, the point being that often times these therapies are things that you can actually do better on without waiting for the chemotherapy to fail.

Abu-Khalaf Right, when these drugs are early on in development, typically part of the eligibility criteria is that you have had at least had 1 to 2 prior lines of therapy. But you are correct in saying that you do not have to exhaust every single chemotherapy available before you go on to the study.

Gore You mean there are rules for the study about who can go on?

Abu-Khalaf Yes and typically for the patient's safety and to make sure that you can actually get results from the trial that will lead you to think that it is either positive or negative. There is a check list, it is an eligibility criteria so it says that you have to have metastatic breast cancer that is ER positive or ER negative, that you have to be able to measure the tumor and it should be a centimeter or greater so that you can follow it on subsequent scans. It has to say that your liver function and your heart function are adequate because we want to make sure that the patients are safe and we are not

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giving a drug that might affect the liver to somebody who has liver disease. So there is a check list and the research team typically screens, we call it a screening phase, so when a patient comes in we talk about the standard treatments, and we say, I think this is a study that may be good for you. Let us check and make sure you fit the criteria and your labs fit the criteria and when they do, then we say this is something that we can offer you. We give a consent form which is a document that reviews what the patient is going to go through, what the risks are, the side effects, the schedule, the benefits and of course we talk about that as well when we are sitting in the office. For the most part, we give them the consent, they go home, they read it, they come back with questions, we sit again, we address any questions or concerns and if the patient wants to go on the clinical trial and feels that is something that is good for them, they sign the consent in the presence of the research nurse or the physician, or both and then that is when we start all the procedures getting the blood work that is needed, the CAT scans, the MRIs if needed and then we schedule a day to start treatment just as we would for any standard treatments.

Gore Is it much more complicated than if they were getting standard therapy, it sounds like there is a lot going on.

Abu-Khalaf It might be a little bit more, I would not say complicated, it is a busy time in the first couple weeks because we need to do things that we typically would do with standard treatment and a little bit more, but once you start treatments and depending on the clinical trial, for the most part it is very similar to standard treatments.

Dr. Maysa Abu-Khalaf is Associate Professor of Medicine and Medical Oncology and of Obstetrics, Gynecology, and Reproductive Sciences at Yale School of Medicine. We invite you to share your questions and comments, you can send them to canceranswers@yale.edu or you can leave a voicemail message at 888-234-4YCC. As an additional resource archived programs are available in both audio and written format at yalecancercenter.org. I am Bruce Barber hoping you will join us again next Sunday evening at 6:00 for another edition of Yale Cancer Center Answers here on WNPR Connecticut's Public Media Source for news and ideas

