

Dr. Lyndsay Harris, Breakthrough Treatment Options for Breast Cancer August 23, 2009 Welcome to Yale Cancer Center Answers with Dr. Ed Chu and Dr. Francine Foss, I am Bruce Barber. Dr. Chu is Deputy Director and Chief of Medical Oncology at Yale Cancer Center and he is an internationally recognized expert on colorectal cancer. Dr. Foss is a Professor of Medical Oncology and Dermatology and she is an expert in the treatment of lymphomas. If you would like to join the discussion, you can contact the doctors directly. The address is canceranswers@yale.edu and the phone number is 1888-234-4YCC. This evening Ed and Francine welcome Dr. Lyndsay Harris. Dr. Harris is the Director of the Yale Cancer Center Breast Center Program and she is an Associate Professor of Medical Oncology. Chu Breast cancer is one of the diseases for which we have made tremendous strides over the past 10 or 15 years. Can you give us an overview of how the prognosis has changed and how it's significantly improved over the last decade? Harris We have been extremely gratified to see that all of the hard work and research that's going on has started to pay off because we now know that breast cancer is a highly curable condition. The cure rates are in the 80% to 85% range based on numbers just from this year from the American Cancer Society. It turns out that over the last ten years breast cancer incidents have been increasing, but breast cancer mortality has been decreasing, and while we were very excited to find that the mortality is going down, we were concerned about the incidence increasing. But in the last two to three years we have actually seen a decline in the incidence of breast cancer as well and the combination of those is leading to very high cure rates; as I said about 80% to 85% for women diagnosed today. Foss Lyndsay, you talk about the incidence of breast cancer and we hear it's 1 in 9 women, does that still hold true? Harris 1 in 9 women is referring to women who live to the age of 85, and so while the incidence is still in that range, perhaps slightly lower based on the recent numbers, the majority of women in the middle of life do not have that high of a risk. Foss Do you think that the increasing incidence has something to do with the fact that more women are getting mammograms now and more cancers are being picked up early? Harris That was a very strong concern in the last decade to 15 years because of the increasing incidence, but what we think is that with this recent decrease in incidence over the last two to three years, we are now over the hump, if you will, of new cases, and in fact, we are actually starting to see a decline in the incidence itself. 3:03 into mp3 file http://yalecancercenter.org/podcast/aug2309_breakthrough-treatment-breast-cancer.mp3 Chu For the benefit of our listeners out there, could you just review the guidelines and the recommendations for screening for breast cancer? That obviously is very important. Harris Yes it is very important and is still an area of some confusion. What's very clear and there is very little controversy about are the guidelines for mammography in women over 50. All of the national bodies recommend annual mammograms in women over 50 without any doubt as to interval or indication. What is slightly more controversial is the lower age range, and many of the bodies recommend annual screening after the age of 40. There are some groups that still consider every other year

screening, but again that is very controversial. Foss Can you talk about the role of MRI in screening? Harris Absolutely, and this is another area of some controversy, but there are clear recommendations that are coming from the educational bodies. The first is that women who are carriers of a BRCA1 or BRCA2 gene, putting them at an extremely high risk of breast cancer, should have an annual MRI if they choose to maintain the breasts, and they should be screened annually with MRI as well as with a mammogram. The use of MRI for screening other groups of women remains controversial. The incidence of new breast cancers is clearly higher, but also the incidence of false positives is clearly higher. It really is a discussion that every woman with the diagnosis of breast cancer needs to have with her physician. In terms of the remaining population, women who aren't at an extremely high risk, we do not recommend annual MRI screening unless there is a very strong family history or some other similar risks like a history of mantle irradiation for Hodgkin's disease. Chu Lyndsay, once a diagnosis of breast cancer is made in a woman, how do you coordinate the care and how do you come up with treatment evaluations for that particular patient? Harris The optimal care for a woman with breast cancer, I believe, is the multidisciplinary approach. The various groups of specialists that are involved in the care of a patient with breast cancer all have a very important role to play. Typically, a woman will see a surgeon at the time of her diagnosis for either a core biopsy from a radiology suite, or done by a surgeon. That person plays a critical role and it then involves other specialists in deciding whether that patient should have surgery first or some form of systemic therapy first. In addition, the radiation oncologist, the pathologist, and the breast imager are all very-very important members of the team to give the woman an optimal recommendation for initial therapy. Foss What you are basically saying is that after the diagnosis is made, a woman should be seen by a multidisciplinary team before making the next treatment recommendation or decision? 6:46 into mp3 file http://yalecancercenter.org/podcast/aug2309_breakthrough-treatment-breast-cancer.mp3 Harris In my opinion that is true, she is best served by making sure that all of the specialists that would potentially offer her care are at the table when she is diagnosed. Chu When do you make the decision whether the patient undergoes surgical resection of the breast cancer as opposed to perhaps getting a combination of chemotherapy and/or radiation therapy beforehand, and then undergo surgical removal of the tumor? Harris The decisions are again typically made at the tumor board when the surgeon, the radiation oncologist, and the medical oncologist sit together with the pathologist and imagers to review each case and decide if a woman is best served by chemotherapy first or the surgery first, or having a specific radiation oncology approach that requires a surgical implant. Foss A lot of terms are thrown around to a patient at this time like ER, PR positivity, and HER2/neu and other things. Can you help the patient to sort out what all of those terms mean and how we use those terms to make those treatment decisions? Harris Well they are very intimidating initially. There are several biological measurements that we make on the tumor that are absolutely essential to allow a patient to make

an optimal decision. The reason for this is that we now know that breast cancer is not one disease, its actually several different diseases, and so knowing these markers helps us recommend treatment A, B, C, or sometimes a novel therapy that's available for particularly aggressive types of tumors. Chu It's interesting as we are now trying to individually tailor our therapies for the different types of cancer, which is now called individualized personalized medicine, in many ways breast cancer is the poster child and still remains the best example of where you can individually tailor the therapy depending upon the ER, PR, HER2/neu status. Harris Ed you're right, and it's been very lucky for the breast cancer community that first of all, we have very strong advocacy that has allowed much of the research to be supported that has led to these understandings of the different biology's, and secondly, we are at a time in our evolution when new-targeted therapies are actually being used in the clinic. While leukemia doctors and lymphoma doctors are probably just as far, if not further ahead in terms of understating the biological markers, in breast cancer we have been lucky to have, at the same time as these new markers have come available, the targeted therapies that we can use against them. This allows us to take an approach where we subdivide different cancers and then offer a therapy targeted against that subtype.10:04 into mp3 file http://yalecancercenter.org/podcast/aug2309_breakthrough-treatment-breast-cancer.mp3Foss Do all women with breast cancer require a surgical procedure?Harris With rare exceptions all women will require some form of surgery during their treatment. They may need initial therapy either in the form of a lumpectomy or mastectomy or they may benefit from treatment that shrinks down the cancer and makes it easier for the surgeon to remove it, and then they would go on to a surgical treatment. However, it's very important to recognize that the cure rate for breast cancer is a combination of the local therapy and the systemic therapy, and that is what makes it so curable. Chu Generally, the systemic therapy that you are talking about Lyndsay is once the tumor has been removed, the patient would then receive what's called adjuvant therapy, which could be chemotherapy, hormonal therapy, or now, a combination of chemotherapy plus some of these novel targeted therapies. Harris Right, and the systemic, or adjuvant therapy, is usually a cocktail which is designed against the subtype of breast cancer that the woman has. We also know though that the same cocktail can be given before surgery with equivalent benefits, so the timing can be either before or after the surgery. Foss Are there any patient's who don't require any adjuvant therapy after their surgical procedure?Harris Some breast cancer patient's do not have a high enough risk to justify additional treatment. In particular, breast cancers that are not invasive, have not gone outside of the ducts of the breast, may not require additional therapy, although even in that case there are potential benefits, for example tamoxifen, to reduce the risk of having a local recurrence. Foss In terms of the issue of mastectomy versus a lumpectomy, that issue has pretty much been resolved such that it doesn't appear to make a difference long term for most women, what do you think about that?Harris It's very interesting because there has been a change in the rates of mastectomy and lumpectomy in

this country in the last few years. Initially it had gone from a very aggressive approach 20 years or more ago to a more conservative approach. Lumpectomies were much more common. Recently, there have been an increasing number of women who have chosen mastectomy, either because they are at high risk due to a genetic feature or because they have chosen to have reconstruction, and both are reasonable options. They give equivalent cure rates in the vast majority of patient's and there are two options that a woman can consider depending on her preferences. Foss This really is an individual choice that women can make in the course of their treatment. Harris Absolutely. Foss And can you just say a little bit about the role of radiation in early stage breast cancer. Harris Radiation is another very important part of breast cancer treatment, and in fact, if a woman undergoes lumpectomy, the vast majority of women are recommended to have breast radiation either local radiation or more broadly involving the lymph nodes. It's part of the package, if you will, of the surgical treatment for a woman who has a lumpectomy. Chu Lyndsay, can you explain for our listeners the reasoning behind giving the radiation therapy after the surgical procedure? Harris For women who have a lumpectomy, we know that remaining breast tissue is still at risk and there may be cells left behind in the breast that were not well enough treated by the surgery that could come back later. We know that giving radiation after the surgery is able to reduce the local risk of recurrence and improve cure rates to equivalent to a mastectomy. Foss You are listening to Yale Cancer Center Answers and we are here with Dr. Lyndsay Harris discussing new treatment options for women with breast cancer. 15:19 into mp3 file http://yalecancercenter.org/podcast/aug2309_breakthrough-treatment-breast-cancer.mp3 Foss Welcome back to Yale Cancer Center Answers. This is Dr. Francine Foss and I am joined by my co-host Dr. Ed Chu and Dr. Lyndsay Harris, Director of the Yale Cancer Center Breast Program. Lyndsay, we talked about early stage breast cancer and the role of radiation and some of the newer therapy that are available. Can you tell us what happens if a patient has metastatic breast cancer? Harris Metastatic breast cancer is a situation when the breast cancer recurs somewhere in the body. Typically, this is in later years after the diagnosis and treatment, several years after a woman has been treated for her original breast cancer, although about 10% of women will present with metastatic disease. In that case, we think of the breast cancer as more of a chronic illness. We know that it is difficult to completely eradicate it, but there are many-many therapies that can allow women to live with her breast cancer and optimize her quality of life. Chu The treatment strategies for women with metastatic breast cancer have changed significantly over the last five to ten years, such that it's no longer viewed as a death sentence, and as you say, this metastatic disease is becoming more of a chronic process. Harris Absolutely, a perfect example of that is a subtype of breast cancer called HER2 positive, and in the last decade, during my career, I have seen that disease go from a lethal, rapidly developing and life threatening disease, to one that is controlled by treatments against the HER2 receptor. These include

Herceptin and Tykerb (lapatinib) and there are many others that are coming down the pipe that are available for these patients. Chu Again, this is part of the so-called targeted therapies that you have mentioned on a few occasions already. Harris Yes, and is really a shining example of how when you get the right target and the tumor is dependant on that target, you can disable the tumor by using therapies that are against it specifically. Foss Are there any other novel targets besides HER 2 that have been developed for breast cancer? Harris There is one that isn't very novel, but is the first biological target, and that's the estrogen receptor. We use that target all the time in women whose tumors over express it. In addition, there are a number of new biological discoveries that tell us that there are other receptors on18:17 into mp3 file http://yalecancercenter.org/podcast/aug2309_breakthrough-treatment-breast-cancer.mp3 breast cancer cells, the EGFR receptor for example, the KIT receptor and other enzymes that we know to be important in making these cancers growth that can be targeted. Chu Lyndsay, at this years ASCO meeting, the large international/national annual conference where we discuss all the latest findings in the oncology world, there was tremendous enthusiasm that came out of a report that our good friend Dr. Joyce O'Shaughnessy discussed. It's talking about the use of an agent called a PARP inhibitor in combination with chemotherapy. Can you tell us a little bit about why this molecule that Joyce was studying seems so interesting? Harris This is one of those very exciting presentations that has everyone's attention. What we know is that PARP inhibitors appear to increase the likelihood that you can kill cancer cells that are BRCA deficient; in other words, BRCA1 deficient. The PARP enzyme stands for poly ADP-ribose polymerase and is an enzyme that's critical in repairing single stranded DNA damage. The BRCA1 and 2 genes are critical in repairing double stranded DNA damage, and so the principal here is that when you block two ways for the cancers cell to repair its DNA, it is sort of like a double whammy. You essentially knock out both of those mechanisms of repair and the tumor cells die very rapidly. Foss Is this particularly relevant for women who have disease that is not sensitive to chemotherapy anymore? Harris It appears, based on Joyce's data, that the breast cancer patient's treated on this trial had a fairly low response rate to the chemotherapy, but when adding the PARP inhibitor the response rate tripled. Indeed it looks as though a chemo-resistant group of patient's may benefit dramatically from the use of this PARP inhibitor. Chu As I recall Lyndsay, Joyce was studying the combination of this PARP inhibitor with chemotherapy in a special kind of breast cancer, the so called triple negative breast cancer, and you are one of the leading experts in that field. Could you tell us what makes treating this triple negative breast cancer so difficult? Harris Well the triple negative breast cancer is a recently discovered entity that is devoid of good targets, at least so we think. So, having a target for a tumor that is both ER, PR, and HER2 negative is very important. In addition, we know that these breast cancers are more rapidly growing, they tend to recur in younger women and some of them are chemo-resistant, although not all. The triple negative group that Joyce enrolled on the trial actually had fairly21:50 into mp3 file

http://yalecancercenter.org/podcast/aug2309_breakthrough-treatment-breast-cancer.mp3 resistant breast cancer as you pointed out, and adding the PARP inhibitor was highly effective in that group. The reason why we think this group is particularly sensitive is that there are a number of biological studies suggesting that the triple negative breast cancers are actually BRCA null, or they have no BRCA function or limited BRCA function. They are essentially acting like a BRCA1 mutation carriers tumor would. Foss How often does this type of breast cancer occur, how frequent is it? Harris Depending on the group of women you look at, overall it's about 20% of breast cancer, but if you look in younger women, women under 50, in some studies it's as high as 40% to 50%. Chu Lyndsay, your group interestingly enough is also studying the same PARP inhibitor that Joyce reported on recently at the ASCO meeting. Can you tell our listeners what the clinical study is that you folks have focused on? Harris We were very interested in the idea that this PARP inhibitor could be used in tumors that had BRCA1 loss, and certainly the triple negative breast cancers are very good candidates because there is evidence in the laboratory that they have BRCA loss, but in addition, our own cancer center has discovered, Dr. Peter Glazer's laboratory has discovered, that certain breast cancers that are hypoxic have also got evidence of BRCA loss. The design of our trial is not limited to triple negative breast cancers; it includes all breast cancers because we believe that many of the subtypes do show hypoxia. The design of this trial is using a drug called irinotecan, which is able to induce single stranded DNA damage along with the PARP inhibitor to block the repair of that damage in a group of patient's that we think will be particularly vulnerable due to BRCA loss. Foss Is this trial available to any women with breast cancer, or are there specific eligibility criteria that need to be met? Harris As with our trials there is some eligibility criteria. The eligibility for this study is women need to have advanced metastatic breast cancer and they can have had only up to two prior chemotherapy regimens for their metastatic breast cancer. Foss Just to clarify for our listeners, the PARP inhibitors are investigational drugs at this point that are only available to patients who are on a clinical trial. Harris That's absolutely right. They are not approved by the FDA or available off of a study. 24:52 into mp3 file http://yalecancercenter.org/podcast/aug2309_breakthrough-treatment-breast-cancer.mp3 Chu

Certainly the hope is that with continued trials like the one that Joyce presented and the study that you are conducting at Yale Cancer Center, hopefully in the not to distant future, these PARP inhibitor compounds will eventually find their way into part of standard of care treatment regimens. Harris Absolutely, and I would say that we are all extremely excited about these data and hope that they will be reproduce in a second study and then rapidly made available to patients. Foss Lyndsay, can you talk a little bit about when women with breast cancer, particularly metastatic breast cancer, ought to consider participating in a clinical trial? Harris That's a really important question for every patient to ask themselves at every stage of their disease. I think that up till now folks have not thought as much about clinical trials, but we realize that clinical trials are important for the

treatment of each patient if she has an opportunity to potentially improve her treatment options. Not every woman would elect to go on to a clinical trial, but it's extremely important to find out about what trials are available for your particular situation. Foss And how do you do that? Harris There are a number of ways to find out about clinical trials that are available. The NCI has a website that allows you to search all clinical trials that are registered. In addition, the Yale Cancer Center has a website where you can look at what trials are available at our institution and patients I think should avail themselves of these resources. Foss On a brighter note, can you talk a little bit about survivorship with breast cancer? A lot of women are now cured of their breast cancer, so is that the end of the story or should these women still be involved in these survivorship clinics that are ongoing? Harris It's incredibly important to consider survivorship issues because as you said 80% to 85% of women are now cured. Despite the great news about the rate of cure, we know that many women suffer from long-term effects from the treatment and also from having had the diagnosis in the first place. A nurse practitioner, a psychologist, an exercise counselor, or a dietician provides a patient with a comprehensive view of their treatment and recommendations for the future. Chu Lyndsay, it has been great having you as always and we look forward to having you back on a future show with the latest about your PARP inhibitor trials as well as other clinical trials. 27:51 into mp3 file http://yalecancercenter.org/podcast/aug2309_breakthrough-treatment-breast-cancer.mp3 You have been listening to Yale Cancer Center Answers and we would like to thank our special guest this evening Dr. Lyndsay Harris for joining us. Please join us again next Sunday evening, when we will discuss the prevention and diagnosis of early stage melanoma with our guest Dr. David Leffell. Until then, I am Ed Chu from Yale Cancer Center wishing you a safe and healthy week. If you have questions or would like to share your comments, go to yalecancercenter.org where you can also subscribe to our podcast and find written transcripts of past programs. I am Bruce Barber and you are listening to the WNPR Health Forum from Connecticut Public Radio.