

Dr. Harriet Kluger, Innovations in Melanoma Treatment March 22, 2009 Welcome to Yale Cancer Center Answers with Drs. Ed Chu and Francine Foss, I am Bruce Barber. Dr. Chu is Deputy Director and Chief of Medical Oncology at Yale Cancer Center and 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. Harriet Kluger. Dr. Kluger is an Associate Professor of Medical Oncology and a member of the Yale Cancer Center Melanoma Program. Chu Why don't we start off by describing what melanoma is? Kluger Melanoma is a cancer that normally originates in the skin. We all have pigmented cells inside our skin which is what gives our skin its color. Sometimes, these cells cluster and you get moles. So, melanoma typically arises from these pigmented cells, either from a mole or in an area where there was no preexisting mole. It can, however, also come from areas that are not exposed to the sun such as the palms of the hands and the feet, underneath the nail beds, the mouth, the perianal area, and so on. Foss How common is melanoma? Kluger It is interesting, melanoma is a disease that is increasing the most among all cancers over the past five decades. About 62,000 new cases are diagnosed every year in the United States, up from around 40,000 twenty or thirty years ago. Foss I'm pretty sure I know the answer to this question, but what causes melanoma? Kluger There is a genetic component and there is also an environmental component. The worst environmental component is sun exposure, or exposure to any kind of UV radiation such as tanning parlors and so on. Chu What accounts for this significant increase that we have been seeing in melanomas? Is it because the youngsters out there are kind of worshipping the sun a little bit too much and we have too many tanning parlors? Kluger We think that is definitely a contributing factor. The other contributing factor is the increased awareness, so people are going to the dermatologist and we are finding more, and some of these melanomas may in fact not be fatal, but one never knows. People are going to the dermatologist, having things removed that perhaps 20 or 30 years ago would have gone undetected. But the incidence of death from melanoma is also going up and I think that is the 2:30 into mp3 file http://www.yalecancercenter.org/podcast/Answers_Mar-22-09.mp3 strongest evidence that there is a true increase in the incidence, not just an increase in diagnosis. The most likely cause is the change in our lifestyle; people spend more time outside, more time on sailboats, and go on vacation to the equator. People with fair skin probably have no business living in very warm places, but that is what has happened over the past 100 years. In fact, the country that has the most melanoma in the world is Australia. The main reason for that is because you have a bunch of people of Irish descent and fair skin who are living near the equator and they are outdoors a lot. Chu What about here in the State of Connecticut, which obviously does not have the same degree of sunlight exposure as say Florida, Arizona, or Australia? Kluger The incidence in the northeast is slightly lower than places like Arizona and

Texas, but apparently the ozone layer is a little bit thinner over Connecticut, so there actually is a fair amount of radiation over here despite our latitude. Foss Can you talk about exposure in terms of at what period of your life you are at the highest risk? People have said that the exposure you have as a child predisposes you later on in life to develop these kinds of skin cancers. Kluger So that is one of the theories. The problem is that it is very hard to prove that theory. There are a couple of population studies that have looked at the migration of people from one place to another. For example, there was a study done in Israel on people who were born to orthodox Jewish families, where they tend to be very well covered, and they compared that population of patients to people born in secular families who are out on the beach a lot. Then, there was a third population of patients who became orthodox when they were around 20 years old. It turned out that the incidence of melanoma among the people who became orthodox at age 20 was about the same as those who were born to the secular families. But the study was relatively small and there have been a couple of other similar studies, but it is very hard to prove it. We also do not know for sure that what somebody does when they are 30 is not going to influence the skin at age 60 or 70, because now people are living longer. But certainly exposure at a young age is probably the biggest risk factor for melanoma. Foss You talked about melanoma occurring in non-sun-exposed areas of the body, how do we explain that? Kluger It is probably just like any other cancer for which we do not really know why it happens. It is something called the spontaneous mutation in a gene, something goes wrong for reasons that we cannot explain, but there are no known risk factors for non-sun-exposed areas of5:08 into mp3 file http://www.yalecancercenter.org/podcast/Answers_Mar-22-09.mp3 melanoma. There are a couple of genes that have been shown to be abnormal in patients who tend to get melanoma all over their body, but it is normally skin melanoma. Chu What would be the most common age at which the risk for melanoma is the highest? Kluger People get melanoma at all ages. It has now become the most common malignancy diagnosed in women in their thirties and men in their forties, but diagnoses happen in old age as well. The peak incidence is around age 60, but that is because people are living longer now. Foss Harriet, can you talk a little bit about what patients should look for? Because you know we all have these pigmented lesions, these things that we call moles and birthmarks, how do we know whether or not we need to worry about those? Kluger There is something called the A, B, C, D, E criteria, and we are going to add F as well. "A" stands for asymmetry, so any mole that is asymmetric. "B" is the border, so if the border is irregular as opposed to a regular border. "C" is color, so a lesion that has more than one color is suspicious of something that is becoming malignant. "D" is diameter, the diameter of over a half a centimeter, which is around a quarter of an inch, is more likely to be malignant. "E" is elevation of the lesion, and "F" actually stands for funny looking. I know that is a very poor description, but anything that is changing and looks strange. I asked my dermatologist, Dr. Suguru Imaeda, who has a personal interest in screening

and diagnosing melanomas, how often he is surprised by a melanoma. He said approximately once a month he removes something that he did not think was going to be a melanoma in the first place. It is sometimes very, very difficult and the hardest ones to diagnose are those that have no pigment at all, called amelanotic melanoma. They tend to be pink, and most often the patient will bring those lesions to the dermatologist's attention because they are bleeding, they are itchy, or they are just a little bit uncomfortable for some reason. Chu Harriet, what colors should one be particularly concerned about? Kluger Black, and anything that is changing, so more than one color within a lesion. Things that are uniformly brown are normally benign. Foss Does it make any difference whether it is a bump or whether it is a flat lesion? Kluger There are some melanomas that are flat, so that just adds to the confusion. Bumps are generally speaking more likely to be malignant, but a flat lesion that is changing, especially those that are big, can be melanoma too. 7:44 into mp3 file http://www.yalecancercenter.org/podcast/Answers_Mar-22-09.mp3 Chu

If anyone has a funny-looking lesion, the "F" criteria, what should one then do? Kluger One should go to a dermatologist and have it biopsied. Family doctors can biopsy it as well; it depends on the person's ability to access healthcare. People who have fair skin, and people who have a family history of melanoma, should be seeing a dermatologist at least once a year for screening, just like people who should have a Pap smear once a year and a breast exam once a year and so on. Foss Can this occur in children as well? Kluger Yes, but we rarely see melanomas in children. Those tend not to be related to sun exposure. Foss Once a patient knows that they have a melanoma and it has been excised by the dermatologist, what happens next? Kluger Once they are told that it is truly a melanoma we do something called a wide local excision. We take skin around the lesion, just in case a couple of cells have escaped. I do not do it, but the surgeons do it, and over the years this has dramatically decreased the likelihood of recurrence within that same area. They do a wide local excision and then, if the depth is greater than a certain depth and has a greater level of invasion to the structures within the skin, they will also remove lymph nodes in the area that drain that particular lesion. Chu And the surgeon that does this operation is a surgeon who specializes in skin cancer? Kluger Correct. In some places it is a surgical oncologist that does it, in other institutions it is a plastic surgeon. At Yale, we have plastic surgeons typically do this, and the two surgeons that are most focused on are Dr. Ariyan and Dr. Narayan, they spend all of their time doing melanoma-related surgeries. Foss How often do these melanomas spread? Kluger At the time of diagnosis, around 10% spread to other organs; the lymph nodes or internal organs. Most of them are diagnosed as skin only. Foss Do patients need blood work and CAT scans if they have a diagnosis of melanoma? Kluger It depends on the depth of the melanoma, or whether the melanoma is ulcerated. There are a few other features that the pathologists look at under the microscope to help us determine 10:02 into mp3 file http://www.yalecancercenter.org/podcast/Answers_Mar-22-09.mp3 what we call the risk of recurrence. Typically if the risk of recurrence or

metastasis is higher than around 20% or 30%, we will get CAT scans on patients. If it is around 20%, we do chest x-rays periodically, and if it is less than 20%, we tend not to. We do blood work periodically on these people as well and sometimes we pick up metastasis by blood work. Chu When would a patient be referred to see you and to get your input as to what should be done? Kluger That too is somewhat institutional dependent. Here, we tend to follow the patients when they have earlier lesions because the surgeons are so busy and we want them to spend their time doing these wonderful surgeries that they do on the patients. Therefore, the oncologist here will follow the patients more frequently than at some other places in the country. Generally speaking, anything over 2 mm in depth, at Yale it is over 1 mm in depth with ulceration, depth of invasion, and lymph node involvement, certainly we would follow. Chu The melanoma group, of which you are one of the senior members, has a team of doctors that get together and discuss many of the cases. Kluger Yes. It is actually the highlight of our week; we call it Melanoma Breakfast Club. Every Thursday morning at 8:30 we get together with a dedicated surgical pathologist, Dr. Demetrios Braddock, and Dr. Marcus Bosenberg a dermatopathologist who is a new recruit to the melanoma program and is also a lab researcher. We have two surgeons that come, Drs. Ariyan and Narayan, a medical oncologist Dr. Sznol, and Dr. Leonard Farber from the Community Group and Dr. John Rhee also attends. We have radiologists and dermatopathologists who come along as well. We tend to discuss patients and there are sometimes difficulties with management. It is an excellent forum for us to interact with each other at least once a week. We also have the opportunity to discuss research programs and clinical trials. It is a wonderful conduit for getting things from the lab translated quickly into the clinic and vice versa. Chu I would think that having this multidisciplinary team approach is also a great opportunity for patients to get the input of everyone so that they get the best treatment plan. Kluger Yes, and we all have different opinions. We do not always reach a consensus, but that is correct, if a specific patient is coming in to see one oncologist, and gets presented at the tumor board, they may be getting second opinions from another three or four people. For us as well, when it is not clear cut what needs to be done, it is nice to be able to discuss the patient with the group. 12:55 into mp3 file http://www.yalecancercenter.org/podcast/Answers_Mar-22-09.mp3 Foss We talked a little bit about how we diagnose melanoma and the test that we do to see whether or not it has spread. If it does spread outside the skin, generally, where does it metastasize? Kluger The rule with melanoma is that all bets are off. It can go anywhere and we never cease to be surprised. We have seen things come back 22 years later, 25 years later. We have seen melanoma go to odd places like the small bowel, the spleen, and so on. The most common sites of metastasis are within the skin, either between the melanoma and the lymph nodes that drain that area, or within lymph nodes in that area or elsewhere, and the lungs are another common site. The most difficult sites to treat are the liver and brain. Foss Do you ever do surgery on these metastases? Kluger Yes. There is some evidence that

if a patient has a single metastasis, removing that metastasis will probably improve the survival of the patient. We definitely try to go after isolated metastasis surgically when possible. Foss It sounds like a patient who has had a melanoma pretty much has to worry about that for the rest of their life. Kluger Yes. Unfortunately, patients have to then basically incorporate follow-up and the concern into their lives. It becomes a part of who they are and what they do it, and it is somewhat stressful for some people, but with time they get used to it. I always try to tell patients to put this into perspective. If it is a 1-mm melanoma with a 10% chance of recurrence, the risk of that recurrence is not much greater than getting breast cancer or colon cancer, and it is certainly smaller than the risk of getting heart disease. Unfortunately, we have a lot of things that we need to worry about in life and it is just added to that list. Chu The follow-up would be with the dermatologist, the medical oncologist, the surgeon, or a little bit of everyone? Kluger We try to make it as easy for the patients as possible. The follow-up with the dermatologist is predominately to look for a second melanoma. Once a person has had one melanoma, the chance of getting a second one over their lifetime is around 10%. The dermatologists are better than we are at looking at the lesions on the skin and all the odd locations that melanoma can pop up. The follow-up with us is to look for a recurrence of that particular melanoma, and we work with the surgeon, so patients follow-up either with us or with the surgeons, but we do not duplicate that. Foss Does it make any difference for a patient once they have already had a melanoma, to start 15:35 into mp3 file http://www.yalecancercenter.org/podcast/Answers_Mar-22-09.mp3 avoiding sunlight? In other words, can you decrease your risk of developing a second melanoma by decreasing your exposure to ultraviolet radiation? Kluger We do not know that for sure. There is no strong evidence that not going out in the sun makes a difference when somebody has had one melanoma, but particularly if it is a young patient, one would not want to take that risk. If you have a 30-year-old with one melanoma who goes out in the sun, maybe that will impact something that happens 30 years later. Foss So the message is to continue to use your sunscreen. Kluger That is a whole different topic, sunscreen really makes a difference. Foss Thank you very much for this part of the discussion. You are listening to Yale Cancer Center Answers and we are here discussing melanoma with Dr. Harriet Kluger. 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 our guest tonight Dr. Harriet Kluger, a medical oncologist at Yale Cancer Center. Harriet, we were talking a little bit about sunscreen and the fact that even if one has had a melanoma, one potentially could decrease their risk of secondary melanomas later on in life by using sunscreen. What is your recommendation to your patients? Kluger I tell my patients to take maximum precautions, and not just the patient, but their family members and particularly their children. You asked earlier about sunscreen. There have been a couple of studies that showed that in communities that first used sunscreen in the United States, in the southern states, the incidence of melanoma went up, while the incidence of basal cell cancer and squamous cell cancer declined

dramatically. The thought is that people do not burn that much anymore because they use sunscreen and that sunscreen does help to18:03 into mp3 file http://www.yalecancercenter.org/podcast/Answers_Mar-22-09.mp3 decrease the risk, but people get this false sense of security and they spend more time outdoors. We recommend covering yourself with clothing, hats, and so on, and trying not to go out in the sun in the middle of the day, but rather going to the beach in early morning and late afternoon. We look at sunscreen as the last line of protection against the sun. It is not clear whether it makes much difference if you go up on the SPF above 30; we think that any additional SPF probably makes very minimal difference.Chu It is interesting because we very rarely see dermatologists that have a bronzed tan, they usually are pretty pale and seem to follow their own advice.Kluger I think so. I certainly follow my own advice.Foss We did not touch on this, but I think it is an important point, and that is patients who have dark skin, African-American patients and other populations with dark skin. Are they at the same risk for melanoma, and should they follow the same precautions with sunscreen?Kluger We do see African-American and Hispanic patients with melanoma. It is not all that common, but we do see them. Normally it is a non-sun-exposed area, so it probably does not have anything to do with sun exposure. African-Americans have a much lower risk, and probably do not have to follow the same precautions as Caucasians. For Hispanic people, their skin color can vary a lot. In southern Connecticut we have a lot of Italian people, and we see our fair share of Olive skin-colored people who have melanoma. I would say that these precautions should be used for everybody, perhaps with the exception of very, very dark skinned people.Chu Let's get back to the different treatment options. If a patient has a metastatic melanoma that has spread to various organs, what would be the typical approach you would recommend?Kluger We treat every patient individually. It depends on the patient's age, other medical problems, where the disease is, and we have a risk assessment of how aggressive we want to be and whether the treatment is going to be worse for an individual patient than the disease. Some patients have relatively slow growing melanoma and might actually live a long time with their metastatic melanoma even if we do nothing. For those patients, we do not want to take out all of our big guns and give them aggressive therapy that might make them worse off. But certainly for younger patients, patients who have no heart disease, and no lung disease, we try to go for aggressive therapy. Our standard approach at Yale is that if a patient has what we call a good performance status, in other words they are very functional and have no other medical problems, specifically no heart disease and no lung disease, we give them a therapy called high-dose interleukin-2. This is an inpatient therapy; it is difficult to tolerate. 20:55 into mp3 file http://www.yalecancercenter.org/podcast/Answers_Mar-22-09.mp3 Yale Cancer Center is the only place in the state that gives it as far as I know, or gives it frequently, and with that we have a cure rate. The cure rate is relatively small, but we do have patients that we treated many, many years ago who have never had a recurrence. So, that is the first thing that we try. If that does not work, we then try multiple other things. There is an experimental

therapy called ipilimumab. It is a very interesting drug that has been developed by Medarex and Bristol-Myers and hopefully will be FDA approved soon, because we are seeing a similar phenomenon. We have a subset of patients who were treated four, five, six years ago, and have not had a recurrence. There are a number of side effects that go along with it, but certainly we have a share of patients who are doing well. Foss These are both immunotherapies, can you comment a little bit about the role of immunotherapy in this disease and explain a little bit about what these immunotherapies are? Kluger These two therapies are what we call nonspecific immunotherapies. What they do is they rev-up the immune system in a general fashion and then you hope that the immune system will fight the melanoma. When you do that, you also get something called autoimmune disease where the immune system is starting to attack parts of the body that it should not be attacking, like the bowels. People can get diarrhea, rashes, and sometimes these side effects can be fairly severe. There are other more specific immune-based therapies where one gives either a vaccine at the same time to certain protein, or you can remove immune cells from the body and sensitize those cells outside of the body, then put them back into the patient. But you sensitize them to the patient's own melanoma or to specific proteins that are only present in melanoma cells. Those therapies we're not doing much right now at the Yale, but we certainly hope to do them in the future. Foss A couple of these treatments, interleukin-2 and interferon, are substances that our bodies make, so why is it that our bodies are unable to fight these tumors if they make these substances? Kluger We are not making enough, because if we were making lots of interferon and interleukin-2 all the time, we would be walking around all day long as if we had the flu. When one has the flu, part of what one feels, like the fevers, fatigue, and the muscle aches, are not from the influenza virus itself, but from the body responding to that, and that is essentially what we do when we give these therapies. Patients feel like they have the flu, they get fevers, they do not feel well, but if you are doing that in a controlled setting for a limited period of time, it is tolerable and doable. Chu Harriet, as you know both Dr. Foss and I were at the National Cancer Institute many, many moons ago where interleukin-2 was developed, and everyone who received that treatment^{23:45} into mp3 file http://www.yalecancercenter.org/podcast/Answers_Mar-22-09.mp3 had to be admitted to the intensive care unit and patients got really sick. As I understand, you and Dr. Sznol have modified the interleukin-2 such that patients do not get that sick and they do not need to go to the intensive care unit. Can you tell us a little bit about your new approach to that treatment? Kluger This stemmed from necessity. A few years ago, when we wanted to use interleukin-2, it turned out that we did not have enough available intensive care unit beds to admit patients on a regular basis to give the interleukin-2 in the intensive care. It used to be given, and has been given, three times a day at the National Cancer Institute and at other places, and that is just the way that regimen was developed. Nobody ever tried to see what happened if you gave it twice a day, so we started giving it twice a day. It turns out that it makes no difference, response rates are the same, in fact a little bit better, although that might just

be by chance. But certainly we have seen a nice share of responses. Therapies given on the floor, we have to transfer patients to the intensive care unit approximately 10% of the time if they get into trouble, but that is much easier than putting a hundred percent of the patients in the intensive care unit. Foss Are there other treatments available for a melanoma? I know you have been involved in some investigational trials with some drugs and even some oral therapies. Kluger Yes, there are other drugs that we are looking at. There are two ways to treat the cancer cells and melanoma. You can either activate the immune system to attack the cancer cells, or you can try to take a drug that attacks the cancer cells themselves. Chemotherapy, in the classic sense that everybody hears about it, making people nauseous and making their hair fall out and so on, typically attacks cancer cells in an unspecific way and can also affect other cells in the body which is why we have those side effects. Over the past years, the drug companies have been developing drugs that target specific molecules within the melanoma cells that are important for driving those cells. We have tried a few of them, we have a study with dasatinib, a pill that we give for metastatic melanoma, and we have seen some response with that. There is a drug called Sorafenib that was given together with chemotherapy. The national study has just been completed and over 800 patients were accrued, and we are waiting for the results of that. As we go along we are going to see more and more of these specific biological therapies that attack the immune cells. We want to one of the places that is at the forefront of doing that, and one of the drives of the melanoma unit is to learn more about the melanoma cells, what makes them metastasize, and what makes them aggressive. If we can identify those particular markers we can then develop drugs that attack those proteins that are so important in moving this engine of metastasis forward. The big difficulty is that it is not really a homogenous disease, it is a very heterogenous disease, and every patient is different. http://www.yalecancercenter.org/podcast/Answers_Mar-22-09.mp3 We are going to end up having subsets of patients that are going to respond to certain therapies, and in different patients we are going to have to come up with other solutions. Chu One of the unique aspects of the melanoma team that we have here at the cancer center is that it is made up of research scientists working together hand-in-hand with clinical investigators. It has been a very successful model, so much so that in fact your team recently received a very large grant from the National Cancer Institute called the melanoma SPORE, which we are quite proud of. Can you tell a little bit about how this team works to develop new treatment strategies from the laboratory and bring them into the clinic? Kluger I just have to correct you, it is the Yale SPORE in Skin Cancer, because if someone turns on the radio and hears that it is only melanoma, they may be upset. It is not only for melanoma, it is for other skin cancers as well. Credit for getting this award goes to Dr. Ruth Halaban who is our basic scientist that has been coming to the melanoma meetings and tumor boards that we talked about earlier for the past decade, and she sits there and listens to the patient presentations, makes sure that she gets tissue from all the patients so she can grow the cells in the lab, and then studies the cells. She

has pushed this group together and pushed the grant riding. SPORE stands for Special Programs of Research Excellence. It is a National Cancer Institute grant that is around I think 2 million dollars a year, it is a very nice chunk of money, and it goes to a lot of investigators across the institution. Thanks to this particular grant we have been able to bring in researchers from other departments who in the past might not have been that interested in melanoma, but they are now working on melanoma. The SPORE group gets together frequently, we have been very fortunate in that because of the SPORE funding, we have been able to obtain other money as well for research. Chu It is amazing how quickly the time has gone and hopefully we will have you back on a future show to hear more about what is going on with the melanoma team and the SPORE in Skin Cancer. You have been listening to Yale Cancer Center Answers, and I would like to thank our guest expert Dr. Harriet Kluger for joining us this evening. Until next time, 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.