Dr. Harriet Kluger and Dr. Deepak Narayan, Advances in Advanced Melanoma Treatment May 10, 2009Welcome to Yale Cancer Center Answers with Dr. 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 at canceranswers@yale.edu, andthe phone number is 1888-234-4YCC. This evening Ed welcomes Dr. Harriet Kluger and Dr. Deepak Narayan who join us to talk about melanoma. Dr. Kluger is an Associate Professor of Medical Oncology and Dr. Narayan is an Associate Professor of Surgery at Yale Cancer Center.Chu Deepak, lets start off by defining what melanoma is.Narayann A melanoma is a malignancy of the pigment cells of the skin, and unlike the squamous and basal cell, it tends to be a little more aggressive, and hence, merits a little more attention.Chu How common is it? What's the age distribution, and is there any difference in incidence between males and females?Narayann In general, it has been noted that melanoma is among the most rapidly arising cancers in the United States today. That being said, we are seeing a lot of younger patients, in general females, who seem to be more likely to get this, probably because of exposure to the sun; ultraviolet rays. There is another group, predominantly elderly males, and also females who are sun exposed, who tend to get this at a later age. That tends to be a little less aggressive than the younger patients.Chu Harriet, Deepak just said that we seem to be experiencing an increase in the incidence of melanoma; do we know why that's happening?Kluger We think it is predominantly a sun related phenomenon. In the past it was typically men working outdoors, and that's why it was more common in men, but over the years women tend to go out and wear less clothing, especially on places like the legs. Tanning parlors are another problem, also the thinning of the ozone layer. There is less filtering of the sunrays that are coming through and with changes in lifestyle, whereby people are traveling more to exotic and warm places, they are hence getting burned.Chu Typically we think of the places with the highest incidence of melanoma being sunny climates, so the southern part of the United States, and Australia has a very high incidence, but as I understand it, Connecticut actually doesn't have an insignificant number of melanomas; Deepak your thoughts on that?2:59 into mp3 file http://www.yalecancercenter.org/podcast/Answers_May-10-09.mp3Narayan Part of it may be due to the fact that a lot of Connecticut's population does spend its winters down in Florida. That might account for an increased exposure to the sun. As Harriet mentioned, thinning of the ozone layer obviously affects Connecticut as well, and that might also account for part of the increase that we are seeing here at Yale.Chu Are there any genetic risk factors for developing melanoma?Narayann There are a couple of syndromes, familial syndromes, that are associated with an increased incidence of melanoma, but these are very rare, at least in the populations that we see. There are a couple of other diseases that may predispose people to melanoma, one such example is xeroderma pigmentosum, but again the

incidence is extremely low.Chu Say it is a family member, an aunt, uncle, mom, dad, had melanoma. Would an individual then have an increased risk for developing melanoma sometime down the road?Kluger Yes, family history of melanoma is a very big risk factor, whether that's because families tend to have the same lifestyle or whether they share a common gene pool, we don't really know, but there probably are a multitude of other genes that are associated with melanoma that we haven't identified yet. For example, one of the more recent discoveries was the finding of a certain receptor cell in people who have red hair and blue eyes and very fair skin, and those patient's certainly have a predisposition to developing melanoma, but not all family members are going to have melanoma.Chu We all have moles on our skin that can start as early as childhood. In fact, I shouldn't say this, but just two weeks ago my family and I were on a vacation in Hawaii, on the beach, and I noticed my four-year-old had a pretty prominent mole on his arm. Deepak, should we be concerned about these moles. What are the types of skin lesions that one needs to pay particularly close attention to?Narayann In general moles are thought to be benign, in fact all of us have benign moles scattered all over our body. In general we have between 20 to 25 moles, and that's considered normal. The moles that we would be concerned about are moles that are larger than say the size of an eraser on a pencil, larger than 6 mm, moles that have darkened or changed color, have an irregular border, or have bled in the recent past. These are the signs that a mole should be looked at more seriously.Kluger We have what we called the A, B, C, D, E criteria, and we are now adding an F. So, "A" is for asymmetry, just makes it easy to remember, "B" is for border that's irregular, "C" is for6:01 into mp3 file http://www.yalecancercenter.org/podcast/Answers_May-10-09.mp3 color, more than one color within the mole or change in color, "C" can also be for change, "D" for diameter over 6 mm, "E" for elevation, and "F" is for funny looking.Chu So if a mole is very circular in appearance, symmetrical, flat, small, has a brown color, there is probably not so much to worry about.Kluger That's correct.Chu And what is the type of color that one should really pay close attention to?Narayann There is a whole palette of colors that you can see in a melanoma. In general, it ranges from dark brown to black, but having said that there is a very small subset that does not have this pigmentation, called amelanotic melanomas. As Harriet mentioned, the change is also significant. Say for instance you have a really dark brown mole that changes and becomes a little lighter, that would be a cause for concern as well.Chu Are there any particular sites on the body that we need to focus on?Narayann In general, the sun exposed areas are the ones that are most susceptible to it, so the back, arms, and neck areas are the ones that seem to be more exposed to this ultraviolet rays, and therefore, may be more susceptible to it. Having said that, you can get melanomas in your nail bed, on the soles of your feet, even on the scalp, and so, there is no area of the skin that's exempt from developing a melanoma.Chu I had a very close childhood friend who developed choroidal melanoma. Harriet, can you discuss just briefly what choroidal melanoma is?Kluger It's melanoma of the eye. You also see retinal melanomas,

a common site in the eye where melanoma can arise. We think that it's not a sun exposure phenomenon and we think that there is no association with skin melanoma, although we do have a few patients' who have both. You can also get melanoma on the mucosal areas, so the mucosa of the nose, the mouth, the vagina and the anal area. Those are very rare. The ocular melanomas, or the eye melanomas, are around 3% of all melanomas, and the mucosal melanomas are a similar percentage. The skin melanomas are by far the most common form of melanoma.Chu Okay, great. Take us through the process Deepak, if someone is looking at the skin on their left arm, they see, as Harriet would say, a funny looking mole that's large, the color doesn't look right, it looks kind of angry, what should an individual then do?8:48 into mp3 file http://www.yalecancercenter.org/podcast/Answers_May-10-09.mp3Narayan The first order of business is to see someone who is an expert in the diagnosis of melanomas. In general, this turns out to be the dermatologist that the primary care physician will send them to. Once that diagnosis is entertained, the next step is to confirm the diagnosis. That involves both a very comprehensive history and a physical exam, and at the very least obtaining a biopsy from that lesion.Chu When would that individual then go to you?Narayann A patient comes to see me from a dermatologist after a biopsy has been obtained by the dermatologist, that's when I generally get to see them.Chu So the diagnosis of melanoma would be confirmed.Narayann That's correct.Chu That person will then be referred to you.Narayann Right.Chu And then how would you proceed?Narayann The thing about a biopsy is that there is a whole wealth of information that can be obtained from a biopsy, and it's very important that this be done the right way. In general, we try to obtain what's called an excisional biopsy, whereby the entire lesion and a little bit of the tissue underneath it is obtained, and the reason for this is that we need to establish the depth of the melanoma, which gives us very important prognostic information. Now, it may not be possible for all dermatologists to provide this excisional biopsy, hence they end up doing either a shave biopsy, which in a large percentage of times does get most of the lesion. So that's pretty much the way we see most of our patient's.Chu Following the excisional biopsy, is any additional surgery required usually, or is that the end of it?Narayann Right. So the biopsy is merely to establish the diagnosis and to make sure that we are not dealing with another pigmented lesion that could mimic a melanoma. Having confirmed the diagnosis, we have to proceed based upon the depth of the melanoma, and in general, we are guided by certain criteria that have been developed by pathologists and clinicians alike, the so called Clark and Breslow classification. Based upon the depth of the lesion, we advocate a11:11 into mp3 file http://www.yalecancercenter.org/podcast/Answers_May-10-09.mp3 wider excision of the skin around it, and that would be the very minimum for say a melanoma that's gone beyond the skin's surface.Chu Is there a role for lymph node dissection? I know at one point that was kind of in vogue to try to remove the local regional lymph nodes.Narayann The theory behind removing the lymph nodes was that since melanoma was such an aggressive cancer, we would provide significant benefit to the patient's if we prophylactically removed

the lymph nodes. However, lymph node removal is not a benign process, and therefore, we become much more selective about the patient's in whom we do this kind of procedure. What we do nowadays is use a procedure called the sentinel node biopsy. The criteria for these tests are that we have a melanoma that's in general greater than 0.75 mm by the Breslow classification, or a Clark level 4 by the Clark classification. In this procedure, a little radioactive tracer dye is injected into the site and the site of uptake in the lymph node is biopsied and then provides a guideline for further treatment.Chu Harriet, is there any role for further imaging studies to make sure that the melanoma in fact is confined to that local area and hasn't spread to other parts of the body?Kluger Yes, we do additional imaging studies. It does depend on the depth of the melanoma and whether the lymph nodes are involved. Essentially what we do is a risk assessment. We try to decide what the chance is that the patient's melanoma has already spread to other organs before we look for it. So, if someone has a very thin melanoma that's been fully excised, and if the lymph node is negative, or there was no need to even assess the lymph node, we do not do imaging or radiology tests. But if it's a deep melanoma, or melanoma that's spread to a lymph node, we do take a look. We do CAT scans, normally of the chest, the abdomen, and the pelvis, depending on where the melanoma is. Sometimes we will do other things and sometimes if we find a single site to which it spread, we can actually remove that and still cure the patient. That's the reason behind doing the radiology test, to look for things early.Chu Great. You are listening to Yale Cancer Center Answers, and we are here this evening discussing the latest in the evaluation and treatment of melanoma with Dr. Harriet Kluger and Dr. Deepak Narayan from Yale Cancer Center.Chu Welcome back to Yale Cancer Center Answers, this is Dr. Ed Chu and I am joined this evening by our special guest experts Dr. Harriet Kluger and Dr. Deepak Narayan, members of the Yale Cancer Center Melanoma Program. Before the break we were talking about the surgical approach to patients with early stage melanoma. Deepak, can you tell us a little bit more about the special surgical techniques you use for patient's with melanoma?Narayann The great advantage of Yale Cancer Center is that Dr. Steve Ariyan, who was one of the founding members of this melanoma program, and myself, both trained in general surgery and in plastic surgery. As a consequence, removal of these lesions need not be mutilating. For instance, a lesion of the cheek can actually be very easily camouflaged using techniques that are called flaps, whereby incisions are made in the redundant skin adjacent to the melanoma and are moved using special techniques so as to camouflage the incisions so they are not visible to a casual observer. Having said that, it's impossible to provide a flap without a scar, and our aim is to disguise it in natural skin crease lines so that it becomes less visible, therefore, making the patient more comfortable in terms of daily interactions.Chu Great. Kluger I think another instance where you and Dr. Ariyan do an excellent job is when we have melanomas of the ear. Now that people are using baseball caps more and more, I think we have seen an increase in the incidence of melanomas of the ear, particularly the left ear in the United States and the right ear in Australia, because people drive with

their windows open as well.Chu That's interesting.Kluger In order to do a wide excision of the ear, you essentially have to take off a fair part of the earlobe, and the reconstructive work that's done in the melanoma unit by Dr. Ariyan and Dr. Narayan is phenomenal. Sometimes you actually can't tell unless you look very closely, sometimes one will be just slightly smaller than the other, but certainly it's no longer a mutilating procedure in the melanoma clinic.17:00 into mp3 file http://www.yalecancercenter.org/podcast/Answers_May-10-09.mp3Narayan That's absolutely right Harriet. In fact, we have just published a new technique providing for even more hidden scars with specific reference to ear reconstructions and that's planned to be out in the next couple of months.Chu So once surgery is done, is there any role for follow-up chemotherapy or any kind of therapy to be offered to the patient?Kluger Yes, the first thing that we do when we have had a deep melanoma, or a melanoma that spread to a lymph node where we think there's at least a 30% chance the patient is going to develop metastatic disease at some point, we start thinking about whether we should give additional therapy to potentially knock off any tiny cells that might have escaped already at the time of surgery. Unfortunately, the only FDA approved drug for this setting is high dose interferon, which is difficult for some people to tolerate. It's given for a year, intravenously in the office for the first month, and then the patient self-injects up to a period of 11 months. There are a fair number of side effects, not in everybody, but the majority of patient's have some difficulty with it. So, it's not an easy thing for people to do. For that reason, we are also looking for drugs that are more effective than the interferon. We have a number of other clinical trials ongoing at present where we are looking at newer agents to see if we can decrease the likelihood of a melanoma recurring.Chu In patients who don't have a deep melanoma, or whose tumor has not spread to lymph nodes, then there would not be any indication for receiving this adjuvant interferon therapy?Kluger That's correct, we simply follow those patient's with visits, physical exams, blood tests, and sometimes chest x-rays or CAT scans, again, depending on how deep the lesion is.Chu Typically, how frequently should a patient be followed up once a surgery has been done?Kluger If it's a thin melanoma, less than 1 mm, with no adverse features, meaning the melanoma wasn't ulcerated and it was not amelanotic, we will probably see them once a year. If there are any other poor features, we will see them every three to six months.Chu Who would see this patient, would it be you, the medical oncologist? Or would it be Deepak or Steve, the surgeon, the plastic surgeon?Kluger That varies somewhat from institution to institution. At Yale, we tend to follow them in the Medical Oncology Clinic, mainly because the surgeons are so busy that we want them to be able to be in the operating room to increase the flow so that we are able to take care of all the19:42 into mp3 file http://www.yalecancercenter.org/podcast/Answers_May-10-09.mp3 patients in Connecticut. But in some institutions, the thinner melanomas are followed by the surgeons and the thicker ones by the oncologist.Narayann In this context it's important to emphasize that anyone who is diagnosed with a melanoma make it an absolute certainty that they visit their dermatologist

at least twice a year, regardless they get a complete skin exam. I think that's a very important part of the follow-up as well.Kluger Absolutely. The likelihood of developing a second melanoma once you have already had one is at least 10%, and the dermatologist are certainly the experts on doing these full body skin screens and are looking for second melanomas. The follow-up that we do in the oncology clinic is more to look for a recurrence of the melanoma that was already excised.Narayann And I would imagine, maybe this is not correct, but patient's who have had melanoma obviously are at risk for recurrence, but presumably because of their lifestyle they might also be at increased risk for developing the other common forms of skin cancers, basal cell and squamous cell. It's another reason why they should see their dermatologist more frequently.Narayann That's absolutely right.Chu If a patient, unfortunately, were to develop advanced metastatic disease, how do we approach those patients?Kluger Again, it depends on who the patient is, how robust he or she is, and where the melanoma is. If there is a single metastasis, let's say in the lung, there is evidence that resecting that single metastasis does provide some survival benefit. Sometimes we can remove a single metastasis and it may be many years before there is another recurrence, and there may never be another recurrence. If there is more than one metastasis, or if there are locations that are difficult to excise, we then treat patients with systemic therapy, which means treatment that's given either intravenously, or by mouth, and fluid goes to all different parts of the body.Chu What would be your first treatment of choice if someone had disease that involved the lung, the liver, and multiple lymph nodes throughout the body?Kluger If it's a healthy patient, with no other medical problems, no lung disease, no heart disease, we start off by giving a therapy called high-dose interleukin-2. This drug was FDA approved in the 1990s for melanoma, and it's a very tough therapy. We have to hospitalize patients,22:11 into mp3 file http://www.yalecancercenter.org/podcast/Answers_May-10-09.mp3we bring them in for a week, we treat them for a week, send them home for a week, bring them back for another week, and if their disease is shrinking six weeks later, we do the whole thing all over again. Even though it's a tough therapy, the beauty of it is that in a small percentage of patient's we do see what we called durable remissions, so that the melanoma goes away and it can go away for many years. In fact, there were patients treated in the 1980s with this therapy that have never had a recurrence. We are always afraid in the oncology community to use the term cure, but again there is a subset of patient's whose disease never came back.Chu In fact Harriet, as were you, I was at the National Cancer Institute, and during the 80s when interleukin-2 was being developed, all of the patient's required hospitalization admission into the intensive care unit, and they got really sick, but I think one of the really attractive features of what you and Dr. Sznol are doing at Yale Cancer Center, is you are giving this interluken-2, but the patient's aren't being admitted to the intensive care unit, at least upfront, and they are being treated on our inpatient medical oncology ward.Kluger That's correct. Dr. Sznol has modified the regimen a little bit and it seems to be equally effective. We do

treat the patient's on the floor, if their blood pressure drops we tolerate it, we don't sent them to the intensive care unit, approximately 10% of our patient's, however, do end up in the intensive care unit. We feel that it's safe to do it in this fashion and it appears to be as equally effective.Chu One thing we didn't mention in the first part of the program, but I think is important to emphasize to those who are listening, is that all patient's who are seen in the melanoma clinic, either early stage or advanced disease stage, all of their cases are discussed and reviewed by your multidisciplinary team. Deepak, could you mention a little bit about what that's all about?Narayann The multidisciplinary team is now becoming a very important part of cancer treatment across the board. The Yale multidisciplinary team is made up of a wide range of experts such as Harriet and our colleges, Dr. Mario Sznol, and physicians in the community, so medical oncologists, surgical oncologists, and we have radiation therapists. One of the unique features of the Yale Cancer Center Melanoma Group is that we also have research scientists as an integral part of our team, and that helps significantly to answer questions, which may not be readily answered by teams made up of just surgical oncologists and medical oncologists. We also have epidemiologists represented in the team and all together this makes for a very effective treatment group for melanomas.25:10 into mp3 file http://www.yalecancercenter.org/podcast/Answers_May-10-09.mp3Chu In fact Harriet, your melanoma team was successful in receiving a very large grant from the National Cancer Institute as part of the skin cancer SPORE. Can you tell us a little bit about what that means?Kluger About three years ago we were awarded a grant called a SPORE grant, which stands for Special Programs of Research Excellence. There were three melanoma SPORES in the country at that time. Since then, the University of Pittsburgh and the Dana Faber group have also received the SPORE award, so there are five now. Essentially these are large grants with multiple projects and the idea is to do translational research. The group gets together very frequently and any laboratory or research findings can be then translated into clinical trails relatively quickly, and the funding is there and available for this. It allows us to do a lot of very nice research that we were not able to do in the past. For example, one of the key components of our melanoma SPORE grant is that we have a tissue core. Every patient that comes in gets their blood drawn and stored, their tissue gets banked in a special bank, and if years later there is a recurrence of disease or if a new drug is available for a specific subtype of melanoma, we can then characterize that particular patient's tissue and see if they are a good candidate for a specific therapy. This certainly is a feature that's not available everywhere, and we are very lucky to have this. We have other opportunities to do experiments looking at thousands of genes or proteins in a single experiment and we have the statistical infrastructure to help analyze this data.Chu One of the key elements of your melanoma disease team, multidisciplinary disease team, and the SPORE, is really trying to develop novel clinical trials.Kluger That's correct. We have a number of clinical trails. You asked me earlier about the standard of care and we spoke about interluken-2, and then we went to another subject, but let's get back to

what we do when a patient's disease has spread. If a patient is not a candidate for IL-2, or if they have received IL-2 and were not one of the fortunate ones to benefit from it, we have a number of other things to offer them. We have a menu of clinical trails, we look at the patient's tumor and we try to tailor the specific clinical trail to the characteristics of the patient's tumor.Chu It's amazing how quickly time has gone; obviously we will have to get the two of you back for a follow-up discussion on treatment advances for melanoma. You have been listening to Yale Cancer Center Answers. I would like to thank our guests, Dr. Harriet Kluger and Dr. Deepak Narayan for joining me 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.