Dr. Madhav Dhodapkar, A Focus on Multiple Myeloma August 16, 2009Welcome 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 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 Dr. Chu welcomes Dr. MadhavDhodapkar. Dr. Dhodapkar is a Professor at Yale School of Medicine and Chief of the Section of Hematology.Chu Let's begin by defining what this disease is.Dhodapkar Myeloma is cancer of an immune cell called plasma cell. These cells normally make antibodies that help you fight infections, but when they are transformed by cancer they accumulate in the bone marrow and that leads to a disease called multiple myeloma.Chu Does this mean that the disease arises because there is a defect in the immune system of that individual patient?Dhodapkar It is a combination of a genetic change that occurs in the plasma cell that causes that plasma cell to be able to survive, proliferate and increase in number in the bone marrow, and at the same time these people often have abnormalities in their immune system which leads to infections, which are very common in these patients.Chu Is there a genetic component as to why multiple myeloma can occur?Dhodapkar We do not precisely know exactly what specific genetic causes predispose to multiple myeloma at this time, but we do know that several genetic abnormalities can be found commonly in myeloma cells and these involve chromosome translocations that are very common in multiple myeloma cells as well as other mutations, specifically what we call oncogenes that we think probably drive the growth of these tumor cells.Chu What else do we know about the potential causes for multiple myeloma?Dhodapkar Unfortunately, in the great majority of cases, we do not really know what the actual cause of multiple myeloma is at this time. Although, as I said earlier, we do know that a great majority of genetic lesions can be attributed to being responsible for the altered growth and survival as well as drug resistance in this tumor.Chu For a long time this disease really was not very well known, but as many politicians and celebrities have been diagnosed with the disease and have been coming forward and talking about the disease,2:50 into mp3 file http://yalecancercenter.org/podcast/aug1609_focus_on_multiple_myeloma.mp3 it has become better known. Can you give us a sense of how common the disease is, how many people are actually diagnosed?Dhodapkar It is actually quite common, it is about 10% of all blood cancers and the incidence of myeloma in fact has been increasing over the past several years. The current estimates from the American Cancer Society are that about 20,000 cases will be diagnosed with multiple myeloma over this year.Chu Do we know why the incidence of multiple myeloma seems to be increasing?Dhodapkar Not precisely, no. Part of this could be detection, that we are detecting myeloma earlier then we used to, but it is also possible that there are other reasons.Chu What are the typical symptoms and signs of the disease?Dhodapkar In this

tumor most of the tumor cells grow predominantly in the bone marrow and therefore it becomes a very debilitating disease because the major symptom of multiple myeloma is bone pain. This is because the myeloma tumor cells cause lytic lesions, or holes in bones if you will, that cause significant thinning of the bone and can lead to fractures with minimal exertion or activity. The growth of tumor cells in the bone marrow also causes abnormalities in normal blood cells, such as development of anemia, and the development or occurrence of infections or bleeding. In addition, some patients can also develop problems with kidney dysfunction or hypercalcemia and things like that. Chu Now, you mentioned that this is a disease of the bone marrow and that many of the bones can get involved, are there any particular types of bones that may be predisposed for multiple myeloma?Dhodapkar Pretty much any part of the skeleton in fact can, in principal, be involved with myeloma; however, a common site is the vertebral bodies of the spine in the back, so back pain, for example, is a very common feature as well as what we call long bones, such as the femur or the humerus with the arms and legs, and again these can lead to fractures, which can be very debilitating.Chu Recently on the show we interviewed Dr. Mel Goldstein, who is obviously our beloved meteorologist on News Chanel 8, and he has had multiple myeloma for a number of years now and as he said, he has lost a number of inches in height because pretty much all of the vertebral bodies of his spine have been fractured and involved in some form by myeloma.Dhodapkar Correct. Loss of height is in fact a common feature of many patients, primarily because of5:35 into mp3 file http://yalecancercenter.org/podcast/aug1609_focus_on_multiple_myeloma.mp3vertebral collapse that occurs as a result of chronic thinning and weakening of those vertebral bodies.Chu Now, how is the disease diagnosed?Dhodapkar The diagnosis of myeloma is based on two broad approaches, one is to actually take a biopsy of the bone marrow to document the presence of the tumor cells in the bone marrow, as well as an analysis of the abnormal antibody that is made by these plasma cells, which can be detected by a relatively simple test in the blood or the urine. It is a combination of finding increased plasma cells in the bone marrow along with the detection of these abnormal antibodies that these cells make that helps to establish the diagnosis. When we establish the diagnosis, the next step is to try to stage the disease and to understand the degree of involvement of the tumor, and that is often based on a collection of markers that are based on things like serum albumin or a blood test called beta-2 microglobulin. These are tests that help us understand the degree of burden, if you will, of the tumor cells in the body and help us prognosticate the tumor. Furthermore, we also want to be able to understand the genetic changes in the tumor cells, so we think it is very important that all myeloma patients at diagnosis have analysis of what we call cytogenetics, or chromosomal analysis, because different kinds of myeloma can present in a different fashion and it is very important to understand which specific kind of myeloma the patient has to help tailor therapy for that patient.Chu Madhav, you have mentioned that a bone marrow evaluation is part of the initial diagnostic workup, is that a difficult procedure that is painful for patients to

undergo?Dhodapkar It is something that is performed as an outpatient and we do this by providing both local anesthetic as well as a sedative in some cases. In most instances we are able to do this with rather little discomfort, but it does have some discomfort at the time when the actual marrow is obtained, but it is an important part of the diagnostic workup in multiple myeloma and particularly important because we are beginning to appreciate that myeloma, perhaps, is not just a single disease, that perhaps there are different kinds of tumors that all manifest themselves in multiple myeloma and we need to understand the biology of these tumors better so that we can individually treat each patient the appropriate way.Chu Now, as I understand it, myeloma can also affect the kidneys. Is there any test that you do beforehand to try to evaluate whether or not kidney function is affected and whether myeloma is in fact involving the kidneys?Dhodapkar Part of the initial evaluation for myeloma includes assessment of kidney function as well as an8:45 into mp3 file http://yalecancercenter.org/podcast/aug1609_focus_on_multiple_myeloma.mp3assessment of serum calcium and an evaluation of the bones, which is obtained by obtaining x-rays of the bones, and this is primarily to look for what we call end-organ damage in the context of myeloma, which is to make sure that the extent of skeletal health and the kidney organ functions is either impaired or not in these patients.Chu Would you evaluate whether or not the bones are involved even if a patient is asymptomatic and is not complaining of any kind of bone or back pain?Dhodapkar We will often get a bone survey as a part of initial evaluation because it is quite possible that at the initial diagnosis the patient in fact does not complain of anything but he does have a significant potentially impending lytic lesion that could require intervention.Chu Madhav, who would typically do all of these diagnostic tests, would it be the primary care physician, the general internist or would this individual have to come to someone like yourself who is an expert in this disease?Dhodapkar Well, we think that it is important that the initial staging evaluation be as complete and as systemic as possible, because it does have an impact on the eventual staging, outcome, and treatment planning in this disease, and therefore, we strongly recommend that such an evaluation be carried out by a hematologist/oncologist or in a major center where there is significant expertise or experience for treating multiple myeloma.Chu As you say, as we are getting more sophisticated in trying to dissect out the different types of myeloma, obviously the capabilities of a molecular diagnostics laboratory to be able to have all of those sophisticated diagnostic tests really would be quite helpful to make the diagnosis.Dhodapkar That is correct and that is precisely the reason why I think it is very important for the first steps to be the right steps, for a person to seek out initial evaluation at an institution or at a location where such an evaluation is possible.Chu In a very general way, Madhav, could you give us a sense of what the different stages of the disease are?Dhodapkar The basic fundamental difference between two broad subtypes of myeloma, if you will, are the patients with what we call asymptomatic myeloma; these are patients who actually meet the diagnostic criteria for multiple myeloma but are completely asymptomatic. In other words, they do not have any evidence of bone disease,

kidney function abnormalities, anemia, or hypercalcemia. These patients are often observed without any specific therapy and the term we11:42 into mp3 file http://yalecancercenter.org/podcast/aug1609_focus_on_multiple_myeloma.mp3 used to use for those patients was called smoldering myeloma, because the tumor could in fact smolder for a period of time. However, now we do recognize that a great majority of these patients are at significant risk for progression to myeloma, and therefore, a major area of interest at many institutions is to try to explore new approaches to prevent the development of clinical myeloma even in this entity in the context of clinical trials.Chu I am just curious, Madhav, not to interrupt you, I am sorry, but for these patients who have smoldering myeloma, are there any genetic abnormalities, predictive biomarkers, that could identify which will actually go on to the more aggressive form of myeloma or will continue to stay in this smoldering form?Dhodapkar At this time, the criteria that we use to help assess the risk of progression, if you will, is based on the percent involvement of plasma cells in the bone marrow, or the level of the protein in the blood, and in some cases the kind of protein, the kind of monoclonal protein that there is; however, this is an area of ongoing investigation and research as I said earlier, and we and others are in fact studying this very actively. In fact, I lead a national effort to try to better understand both genetic as well as host features that will hopefully tell us which of these patients are going to be more likely to progress to clinical disease requiring chemotherapy versus which of the patients that we should just be simply observing, as they are less likely to require chemotherapy in the future. But this again remains an area of active research and therefore we recommend that many of these patients should be in clinical trials for observation as well.Chu You are here listening to Yale Cancer Center Answers and I am here in the studio with my special guest expert Dr. Madhav Dhodapkar from Yale Cancer Center discussing multiple myeloma. After the break we will get into more details regarding the treatment options for patients with myeloma.Chu This is Dr. Ed Chu from Yale Cancer Center and I am here in the studio this evening with my14:43 into mp3 file http://yalecancercenter.org/podcast/aug1609_focus_on_multiple_myeloma.mp3 guest expert Dr. Madhav Dhodapkar, Professor and Chief of Hematology at Yale Cancer Center and Yale School of Medicine. Before the break, we were defining the different stages of the disease, and Madhav, you were talking about this entity called smoldering myeloma; can you take us through the other stages of the disease?Dhodapkar The current staging system that we use for multiple myeloma is a staging system called the International Staging System that was developed as a collaborative effort across many institutions and across the globe, in fact, and that system classifies patients into three stages; stage 1, 2 and 3, based on the level of serum albumin as well as serum beta-2 microglobulin. It does help identify patients who are at high risk versus low risk, if you will, in response to conventional chemotherapies as well as normal therapies that are being introduced in this disease. An important point I do want to make is that while multiple myeloma is in fact quite common, there is another entity called MGUS, or monoclonal gammopathy of undetermined significance, which

is in fact much more common than multiple myeloma and this is a precursor condition to myeloma that is found in about 3% to 4% of people who are over 50 years of age. It is very common and the current estimates are that about 1% per year of that cohort can transform to become multiple myeloma. It is again, an important area of research to try to understand how this precursor condition actually develops into multiple myeloma and what can we do to prevent disease.Chu But for the time being, for patients who have this MGUS condition, there is no active treatment.Dhodapkar Correct.Chu Madhav, can you begin to discuss what the different treatment options for the patient with myeloma are.Dhodapkar The landscape of therapeutic options in myeloma in fact has changed dramatically over the last several years with the advent of at least four new drugs that have been FDA approved for myeloma in the last several years. The current spectrum of options extends from both chemotherapy and steroids that used to be the mainstay of therapy for a long time, to now include drugs like thalidomide, Revlimid, Velcade or bortezomib, and Doxil, and these drugs are often used in various combinations and together with high-dose chemotherapy and stem-cell transplantation, they form the backbone, if you will, of therapy in most patients with multiple myeloma.Chu It really is nice to see because as you say, when I went for my training, we really only had very toxic chemotherapy plus or minus prednisone steroids, and now it is quite remarkable to see how much the field has advanced with respect of these new therapies.Dhodapkar No question, I feel gratified to have been a part of the original discovery of thalidomide and the17:55 into mp3 file http://yalecancercenter.org/podcast/aug1609_focus_on_multiple_myeloma.mp3 introduction in the context of myeloma. In fact, we just recently published a 10-year update of the first clinical trial for thalidomide in myeloma still showing that we have people alive at 10 years of follow-up out of the original trial, which has been very-very gratifying. But indeed there is no question that these new drugs have changed the outcome, or at least the longterm outcome, as well as overall survival in patients with multiple myeloma across the globe.Chu When people hear the name thalidomide they may feel it is a bit funny because it got very bad press many-many years ago. Can you tell us how thalidomide works for this disease?Dhodapkar The precise mechanism by which thalidomide works is still to some degree not entirely clear. However, what thalidomide and its cousin, Revlimid, represent are a class of drugs that we call immunomodulatory drugs in myeloma or MGUS, but these drugs have changed the paradigm of trying to approach the myeloma by pointing out that perhaps the major target for targeting myeloma is not just the tumor cell itself, but the host microenvironments, that is the normal cells that surround the tumor cells. So, the major targets for thalidomide may in fact be their ability to inhibit angiogenesis or new blood vessel formation or their ability to enhance specific aspects of the immune system, both in native and adaptive immune systems, as well as inhibit inflammatory cytokines. It is quite possible that a combination of these effects, that thalidomide mediates antimyeloma effects, which are very effective and very powerful in the clinic.Chu Are there any significant side effects associated with either thalidomide or Revlimid?Dhodapkar Yes

indeed, thalidomide does have a major side effect of neuropathy, i.e., damage to nerves, which can be debilitating in some individuals and can be dose limiting in some patients. Another major potential side effect of thalidomide is the development of blood clots, particularly when thalidomide has been used in combination with some other chemotherapy type medications; therefore, most patients who receive thalidomide are often also advised to take a blood thinning medication or aspirin or another medication such as low-molecular weight heparin to try to prevent the development of these potentially major complications. I should point out that Revlimid, which is the other analog of thalidomide, does have a lower propensity for causing some of these side effects such as neuropathy. It does have a greater propensity for causing some other side effects, such as lowering blood counts, which may make you more prone to infections or bleeding.Chu We are hearing a lot these days about the role of stem cell transplantation in the treatment of myeloma. When would you consider transplantation for a patient with multiple myeloma?Dhodapkar Stem-cell transplantation in the context of multiple myeloma is still considered part of standard of care, or one of the standard therapeutic options in patients who are otherwise eligible for transplant. What that means is patients who are typically less than 65 years of age and/or have 21:42 into mp3 file http://yalecancercenter.org/podcast/aug1609_focus_on_multiple_myeloma.mp3 good otherwise functional status and might be able to tolerate the procedure. There had been some questions about whether or not transplantation could be delayed in patients in the setting of some of the newer therapies, and that remains an area of active investigation because with the advent of new therapies like Revlimid or bortezomib and the combination, we are seeing fairly high response rates to the combination chemotherapies. It is quite possible that we might be able to delay and/or avoid stem-cell transplantation in many individuals. However, that remains a question that needs to be answered in the context of a defined prospective clinical trial. On the other hand, we already have data from clinical trials that have shown that stem-cell transplantation does prolong survival in multiple myeloma and therefore it does remain a part of standard momentarium of therapeutic options for these patients.Chu You mentioned with respect to thalidomide and Revlimid that they may work in part for modulating the immune system. Your own research over the last many years has focused on trying to understand the immunobiology of myeloma and develop new immunotherapies. Can you tell our listeners what your own research group has been doing to try to attack myeloma on this front?Dhodapkar One of our major areas of interest is to look at the host microenvironment in the context of myeloma. This has been inspired to a large degree by the discovery of thalidomide, because it showed us that the host microenvironment is a very important target in the case of myeloma. What we now realize is that several aspects of host immune response have the capacity to target the tumor cells, and what we need to do is better understand how to harness those properties in the clinic so that we can achieve more durable responses from conventional therapies, or combine those approaches with conventional therapies to improve the efficacy of anti-myeloma therapy. Another important aspect that we are

interested in understanding is the biology of what we call stem cells, or cancer stem cells, in myeloma; only some of the tumor cells may be important for driving this disease. It is important for us to understand what the residual cells are when people are in so called "complete remission" in this disease that are remaining in the body, so that we can specifically learn to target these cells, both immunologically or with drugs, so that we can achieve either a longterm durable state of dormancy in which you are living with the cancer for a long period of time as a chronic disease, or trying to achieve cure by eradicating the last few cells that remain after these current therapies have been applied. As I said earlier, it is now becoming clear that the current therapies do achieve a high proportion of what we call complete responses, but we also know that even in these settings, patients still have tumor cells remaining within their body.Chu It is interesting that certainly for the other solid tumors, breast cancer and now more recently colorectal cancer, there is also a great deal of research trying to understand this issue of cancer stem cells. I think what people are finding is those residual cancer stem cells are truly very25:28 into mp3 file http://yalecancercenter.org/podcast/aug1609_focus_on_multiple_myeloma.mp3 resistant clones of tumor cells that are very-very resistant and refractory to pretty much all of the active drugs that seem to kill off the rest of the tumor cells.Dhodapkar Exactly right. We really need to understand better about this potential Achilles heel of cancer to be able to understand how to eradicate the last few cells, and in fact, we just presented some information at the last ASCO meeting, which is American Society of Clinical Oncology, showing that patients who develop an immune response against some of these so called cancer stem cells have an exceptionally good outcome and that is perhaps the most dominant predictor of outcome in patients with early-stage disease. We are encouraged by some of these studies to begin to think about newer approaches to try to target these cells, either through antibodies or through vaccines, or through drugs that specifically would try to hit these cells at a stage where we have gotten the disease into what we call minimal residual disease. As I mentioned earlier, we are in fact doing, or in the process of putting together, new combinations of biologics, if you will, that combine the old drugs such as Revlimid with some new biologics to try to see if we can improve upon the efficacy of these new drugs. We are also developing new antibodies to try to target these stem cell like cells and cancer. Again, these are studies at early stages of development and only time will tell what the final efficacy of these approaches are, but I think it is very-very important in the context of particularly of myeloma where we are very blessed with lots and lots of options for new therapies and new targets in this disease that patients be treated in the context of clinical trials. I cannot emphasize more the importance of clinical trials and that our feeling as a group is that essentially all patients with myeloma should actually be on a clinical trial or should have access to a clinical trial. The message I want to give is a message of hope, in that myeloma is a disease that has changed from a disease where the survival used to be short and we could not promise longterm survival, to a stage where we can achieve longterm survival. There are people living with the disease and

we are looking at the potential that we might be able to cure a subpopulation of these patients. I think myeloma could serve as an example for other cancers as well, where through research and through participation in clinical trials, we could in fact make substantial strides in tackling even the most difficult cancers that we deal with.Chu Great! You have been listening to Yale Cancer Center Answers and I would like to thank our guest on this evening's show, Dr. Madhav Dhodapkar, for joining me. Until next time, I am Ed Chu from the 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.