

Dr. Francine Foss, New Updates on Lymphoma September 21, 2008 Welcome to Yale Cancer Center Answers with Dr. Ed Chu and Dr. Ken Miller. I am Bruce Barber. Dr. Chu is Deputy Director and Chief of Medical Oncology at Yale Cancer Center and Dr. Miller is a Medical Oncologist specializing in pain and palliative care, and he also serves as Director of the Connecticut Challenge Survivorship Clinic. If you would like to join the discussion, you can contact the doctors directly at canceranswers@yale.edu or 1-888-234-4YCC. This evening we welcome Dr. Francine Foss. Dr. Foss is a Professor of Medical Oncology at Yale Cancer Center and an internationally known expert in the treatment of lymphoma. Foss Most lymphomas are divided into Hodgkin and non-Hodgkin. There are about 8,500 Hodgkin lymphoma cases per year in the United States, as opposed to non-Hodgkin lymphomas, which are the majority of cases. Most of those are B-Cell lymphomas. If you look at all non-Hodgkin lymphomas, 85% of them are of the B-cell type, and only a small minority, 15 %, are T-cell lymphomas. However, if you look overall at the number of lymphomas in the United States, T-cell lymphomas are about 9000 cases as opposed to Hodgkin, which is 8500 cases. You hear more about Hodgkin disease than you do about T-Cell lymphoma. Miller I am really glad you brought up the numbers because we think of Hodgkin's in a very prominent way, perhaps because this was one of the first types of lymphoma that was cured. Foss That is right, Hodgkin's disease was cured in Stanford with radiation and chemotherapy, called MOPP. There have been a lot of therapies directed at Hodgkin lymphoma and now at non-Hodgkin B-cell lymphomas. There are a lot of new therapies that target B-cells, however, T-cells have only recently been recognized and only recently have we had good therapies for these patients. Miller Because T-cell is less common than B-cell lymphoma, how did you get involved? Foss I guess because I like to study rare and unusual things. I got involved when I was back at the National Cancer Institute where we had one of the first programs in T-cell lymphoma, and in fact, it was at that program, at the NCI, that we first discovered the HTLV-I virus, which is the virus that causes acute T-cell leukemia. That was done by Dr. Bob Gallo, and at the time, we were looking at other T-cell lymphomas to see if they had a virus as well, and so I got involved very early on in those projects. Miller Along those lines, this issue of the viral cause of some cancers is very important. What is your finding, are T-cell lymphomas caused by a virus, what causes them? 2:38 into mp3 file http://www.yalecancercenter.org/podcast/Answers_Sept-21-08.mp3 Foss We know that viruses can contribute to B-cell lymphoma, the EBV virus being the most common type, but we can also see EBV virus in various T-cell lymphomas as well. We know that patients who have hepatitis, for instance, can have a higher incidence of lymphoma. We do find this HTLV-1 virus in T-cell lymphoma, but that is fairly rare in the United States. Other than that, we really do not have any close connection between viruses and T-cell lymphoma. Miller Lymphocytes, which are a form of white blood cells, have a certain appearance under the microscope, can you tell the difference between what is a T-cell and what is a B cell under the microscope, how do you know the difference? Foss It is very difficult to tell and the only way that we can really

know the difference is using surface markers. These are proteins on the surface of the cells that we have antibodies for. We can look under the microscope and we can tell whether the patient has a T- or B-cell based on looking not only at one, but a whole panel of markers. The other way we can do it is by looking at the genes themselves. We look for the T-cell receptor, T-cell lymphomas, or the immunoglobulin heavy chain for B-cell lymphomas. Miller With T-cell lymphoma, there is a wide spectrum of how it presents, sometimes it sounds like it is a skin disease, other times a blood disease, can you lay that out for us a little bit? Foss T-cell lymphomas are what I call, the promiscuous lymphoma, because they can occur in a number of different parts of the body and they can also masquerade as other diseases. It is not uncommon for us to see patients that have been misdiagnosed with autoimmune diseases like arthritis or lupus. Some patients have had hemolytic anemia of unclear etiology, and some patients come in with a fever that they have had for weeks or months. Often times it is difficult for the primary care doctor to diagnose T-cell lymphoma because in its earliest stages, it can be very difficult to find. It is only after these symptoms have manifested themselves for weeks or months that we are actually able to make that diagnosis. In cases that I see sometimes the pathologist will tell me that the diagnosis is very tricky. I think that is an important thing for patients to remember because if you do have one of these lymphomas and you have had these symptoms for weeks or months, it is not necessarily that your doctors made a mistake. The disease itself likes to masquerade itself as other things. Miller If you have a patient with T-cell lymphoma affecting the skin, what might you see when you examine that patient? 5:14 into mp3 file http://www.yalecancercenter.org/podcast/Answers_Sept-21-08.mp3 Foss A lot of T-cell lymphomas like the skin because of the characteristics of the cells that make them like to live in the skin, but it is important to remember that even though they are in the skin, they are also possibly in other areas of your body. You cannot trick yourself into thinking that just by treating that skin nodule you are going to get rid of the disease. We do not understand why they like to go to the skin, but if you look at all lymphomas that present in the skin, about 80% of them are T-cell lymphomas. There are some B-cell lymphomas that can also do this, and it is important to remember that. Miller Is it a rash? Foss Well, usually they present as nodules or lumps, but they also can present as a rash. They can look like eczema, psoriasis, or an insect bite. In some cases, we have people that come in with a rash that looks like Lyme disease, but it was biopsied and it was shown to be lymphoma. Miller Interesting, you said two points which I think are really fascinating, one is, promiscuous lymphoma, and the second is that it masquerades. Those are important things to remember. We had an e-mail question from Marsha who lives in Longmeadow, Massachusetts. She writes, "My father had non-Hodgkin disease, and then T-cell lymphoma, is this genetic and do I have to worry about my children?" Foss We do not have a lot of good information to support that these lymphomas are genetic, and in fact, we do have some evidence to support the fact that there are environmental factors that contribute to getting these lymphomas. The only hint we have about a potential genetic predilection is that there has been

work done here at Yale as part of an international effort to look at various genes in patients to see whether any of those genes predict whether the patient is ever going to develop a lymphoma in their life. We have actually picked out a panel of genes that predicts for T-cell lymphoma. This work is being done by Dr. Yawei Zhang in the Epidemiology Department at Yale, and in fact, by looking at these panels of genes, we can start looking at family members to see if there might potentially be a risk in the family, but at this point we really do not feel that these lymphomas by and large are genetic. Miller If we have project 10-20 years into the future, if you know what genes may predict, how might that help you and help patients, eventually? Foss There are two factors here, there is the biological factor and then there is the environment that we all encounter everyday with all of the various chemicals, toxins, and radiation. Many of us in the lymphoma field feel that there is a contribution of environmental toxins and the way the body responds to those. For instance, if we know that you have a pattern of genes that makes it harder to repair DNA damage by these chemicals, for instance, then one might think about a prophylactic or preventive program, using antioxidants or other substances that might help to protect your DNA. The same way that we think about patients with familial colon cancer and familial breast cancer, we know that we need to look in other target organs for other cancers that are associated with those family cancers. Miller Let me ask you, along those lines, one of my cousins has Celiac disease, or sprue, which is a bowel disorder. In that case, does a careful diet reduce his risk of developing lymphoma? Foss It is unclear, but I think most of us feel that because the disease is stimulated by the gluten in the diet, the more of that gluten that your body is exposed to, the more of those T-cells are going to be reacting against it and eventually, if you have lymphocytes, be they T- or B cells that continue to react against a foreign toxin or an antigen, then eventually you are going to select out a clone of cells that will develop into a lymphoma. So, I think the answer is yes. If we are careful about exposure, perhaps we can prevent some of these cancers. Miller Let me ask, this is not quite T-cells as much as maybe, B-cell, but the bacteria in the stomach, H pylori, is a fascinating story. How is that associated with non-Hodgkin lymphoma and can you cure lymphoma by giving antibiotics? Foss Well, that has been a really interesting story for those of us in the lymphoma field because what we have learned is that this bacteria infection in the stomach essentially acts like a foreign antigen and it stimulates an immune response, in this case, of the B-cells, and what happens with that infection sitting there for weeks, months, or years, is that the body develops a very brisk reaction and you develop a clonal proliferation of B cells, which is our definition of B-cell lymphoma. We know that treating that infection with antibiotics and medications that suppress the acid in the stomach actually can cure patients without giving them chemotherapy or radiation. That is really fascinating and has got us thinking a lot about some other things that we are exposed to in our environment. In fact, you can extrapolate from that to look at some of these lymphomas that actually

spontaneously regress. We have seen T-cell and B cell lymphomas that go away without us doing anything, and perhaps that represents taking away some stimulus for the lymphoma that we do not even know about yet. Miller Along those lines, you see so many patients with this unusual, maybe not unusual, but with this specific type of lymphoma. Any stories that you can remember in terms of patients where you saw regression, without chemotherapy? 10:44 into mp3file http://www.yalecancercenter.org/podcast/Answers_Sept-21-08.mp3 Foss

There was a very interesting story about an elderly Italian gentleman who came in with this huge mass on his scalp. It started as a little tiny nodule and got bigger and bigger over about 4 to 5 months, such that it almost covered the entire scalp. He came in to see us and he had a biopsy that showed aggressive T-cell lymphoma, a very aggressive form under the microscope, and so we quickly rushed him to get his CAT scans and his bone marrow biopsy and get ready to give him chemotherapy. Well, low and behold, two weeks later when he came in after getting all these scans done, the lesion looked like it had shrunk down by about 50% and he had done absolutely nothing. We decided to do the conservative thing, which is to wait another couple of weeks to see what happened and low and behold, the lesion completely disappeared and it has never come back again. Miller Wow. Foss That is an important lesson for us as doctors; we need to carefully look at the whole situation and the whole patient before we launch into any therapy. Miller That reminds me of one of my mentors years ago who used to say, "Do you know why they call it the practice of medicine, because we're just practicing?" Does that apply to you and what you have learned? Foss I think that certainly applies to lymphoma, because with the exception of the diffuse large B-cell lymphomas, there really is not any specific treatment paradigm for these diseases. If you look at the low-grade B-cell lymphomas, there are five possible treatments. In fact, the NCCN guidelines, which are national practice guidelines for cancer, do not give us a specific recommendation. They tell us that there are five or six things that you can do and which one you do for a patient really depends on the patient and the doctor and a number of other factors that are intangible. Miller We are going to come back to that in a couple of minutes. For now, we are going to take a break. We encourage you to please e-mail us if you have questions at www.canceranswers@yale.edu. Miller Francine, before we talk about the specific treatments, when you see a new patient with a T-cell lymphoma, how do you make decisions in terms of who needs to be treated, who does not, and what kind of treatment to give, what is the process? Foss What we do is we carefully review the history, and of course the biopsies, and in many cases we will ask for additional tissue so that we can determine the subtype of T-cell lymphoma. That is very important because if you look at the new lymphoma classification system, they have broken T-cell lymphoma up into about 15 or 16 different subtypes, and all of those have slightly different treatments. The first important thing is making the right diagnosis. The second thing is looking at the overall patient and how far the lymphoma has spread. We look in the blood and in bone marrow, and we usually do CAT scans or PET scans. We put all of that information

together and we take the general health of the patient into consideration and then we decide whether the patient should be treated with conventional chemotherapy, radiation therapy, or whether they might be a candidate for one of our investigational studies looking at new ways to approach T-cell lymphoma. Miller Let me throw out a couple of case scenarios. You do all the tests, you do a thorough evaluation, and lastly, you find out of there is a relatively young person, let's say 50 because I am around that age, or little bit older, with early stage single nodule on an area of the skin, how do you approach that? Foss If that is an aggressive T-cell lymphoma, then we may approach that just by radiating the area, but we keep in the back of our minds that these lymphomas do come back, and in many cases with T-cell lymphoma they are not really curable, so we have to be very careful about watching what is going to happen next. Miller And on the other side of the spectrum, a patient let's say who presents with very advanced T-cell lymphoma with symptoms and with enlarged lymph nodes, what is the general approach there? Foss We know that those patients need aggressive chemotherapy and in many cases they need to have 4 or 5 chemotherapy drugs given at the same time. We also know that although half of those patients will go into remission, many of them will relapse, so that is when we start thinking about more aggressive approaches to potentially cure these patients. That includes bone marrow transplantation, be it from you or from another donor. We like to start thinking about that earlier rather than later in a disease that we know is going to recur. If we in fact have a family donor, that would be the preferred approach for many of our patients, but there are patients who are older, who have other medical problems, or who do not have an identically matched donor, and in that case, we need to think of more creative strategies for them. Miller For those that are able to have a bone marrow transplant, what is the advantage of that, what is the mechanism by which it works? Foss There are two types of bone marrow transplant. The autologous transplant is where you give yourself back the cells, and the allogeneic transplant is where you get the cells from somebody else. In the autologous transplant, we would like to take the cells from you at a point where we think your disease is completely in remission, and then we give you very high dose chemotherapy to try to eradicate any residual tumor cells that are still hiding out in the body. Then we give you your own stem cells back to reconstitute your immune system. An autologous transplant is super-duper chemotherapy, whereas the allogeneic transplant has a completely different mechanism. With the allogeneic transplant we are essentially getting rid of your own immune system using our conditioning therapies, and then we are giving you back a new immune system. We are giving you cells from somebody else and those cells hopefully will be able to recognize your tumor cells and any residual tumor cells left in your body and kill them. The allogeneic transplant is really immunotherapy as opposed to the autologous, which as I mentioned, is really super-duper chemotherapy. Miller What are some antibodies for T-cell lymphoma? Foss Antibodies are very interesting and have completely changed the way we treat

lymphomas. An antibody is a molecule that is directed against a protein on the surface of a tumor cell. In the case of rituximab, for instance, rituximab for B-cell lymphoma targets the CD20 protein, which is expressed on just about every B-cell lymphoma. These antibodies are part of the body's own immune system and by binding these antibodies to the tumor cells, it helps our immune system get rid of those tumor cells. So, we have rituximab for B-cell lymphoma and now we have got a number of antibodies for T-cell lymphoma as well; including Campath which is good not only for T-cell but also for other types of lymphoma. Now we have some new unique and interesting ones that are still in investigation; such as the antiCD4 antibody. Miller Along those lines, a lot of your research has been on a fusion toxin that was 8:23 into mp3 file http://www.yalecancercenter.org/podcast/Answers_Sept-21-08.mp3 one of the first FDA approved biological drugs for the treatment of lymphoma. Can you tell us the history of that and what it is? Foss Just like an antibody would bind to a protein on the surface of a tumor cell, a fusion toxin essentially does the same thing, but the fusion toxin is armed with an element such as a toxin that can get into that tumor cell and kill it; whereas the antibody by itself really depends on the immune system to kill the cell. Ontak is a molecule that consists of interleukin 2, which binds to the interleukin 2 receptor combined with diphtheria toxin, so that once that molecule binds to the cell, the diphtheria toxin gets into that tumor cell and it kills the cell. So the IL-2 part of it is a carrier; a way of delivery in that molecule specifically to tumor cells that have the IL-2 receptor. Miller When the diphtheria toxin is, in a sense, delivered, almost like a Trojan horse to the cancer cells, what happens then? Foss The diphtheria toxin is a very potent toxin and if you just get one molecule into a cancer cell, it will kill that cell. So, it is a very, very effective way of killing cancer cells. Miller Is the diphtheria toxin delivered in normal cells? Foss The delivery of diphtheria toxin is very selective based on the IL-2 part of that molecule. The IL-2 part will deliver it only to cancer cells or cells that have the IL-2 receptor. In our body there are only a few circulating T lymphocytes, normal ones, that have the IL-2 receptor, otherwise, our normal tissues do not. Even though those few normal T cells are targeted by the molecule, they reconstitute themselves very quickly, so it really does not have any major impact. Miller It sounds like a wonderful approach to treatment to be able to be that selective. We have an e-mail from Michael who lives in Groton who is on the other side of the spectrum from the very intense therapy. He said, "My uncle was just diagnosed with a T-cell lymphoma and his doctors are recommending a watch and wait approach. Is there a role for careful observation?" Foss I think there is definitely a role in B-cell lymphoma for watch and wait; for the low-grade B-cell lymphomas. In T-cell lymphoma it really depends on the subtype. Many of these patients do need to go on to therapy, and the nice thing about T-cell lymphoma is that we have a number of oral drugs that are available now. For instance, we have an oral retinoid molecule called Tagretin that is a derivative of vitamin A. We now have oral HDAC inhibitors, and the one that was recently approved by the FDA is called vorinostat, which is a biomodulator, and

it works by effecting the transcription of genes. So both21:08 into mp3file
http://www.yalecancercenter.org/podcast/Answers_Sept-21-08.mp3Tagretin
 and Zolinza are biological oral therapies that do not have a lot of side effects
 for patients. These are very nice drugs to use in an early stage patient.Miller
 How does Tagretin, which is a form of vitamin A, work?Foss It is a form of
 vitamin A that is modified slightly, chemically, so that it binds to cells. It
 affects the transcription of various genes such as genes that turn on cancer
 cells, so if you can turn off these genes that are driving those cancer cells to
 divide, then you can essentially put the cancer in remission.Miller Francine,
 you are very active as an investigator, what clinical trials are you working
 on?Foss We are working on a number of different clinical trials for T-cell
 lymphoma. One of the interests in our group is trying to develop a new
 therapy for patients when they first come in. What we have done is we
 have taken the conventional chemotherapy called CHOP, and we have added
 the Ontak molecule to that. So, we are giving combined therapy with the
 biological agent in chemotherapy when patients first come in, and we know
 that by doing that about 90% of our patients will have a complete response,
 or a very good response, to their chemotherapy. We are also working on a
 number of drugs that are important for patients who fail chemotherapy, second
 line agents, and we have a couple of new histone deacetylase inhibitors. One
 of them is romidepsin, and the other one is Belinostat, and these are slightly
 different from each other but they both have very significant activity. In
 addition, we have worked with a couple of other new drugs such as pralatrexate,
 which is a new derivative of methotrexate, a very old drug. Pralatrexate
 has a very high activity in T-cell lymphoma and hopefully that drug will
 be FDA approved this year. We are also looking at some new drugs that
 we think might be active in T-cell lymphoma. One of these drugs is called
 chlofarabine and another one is called Treanda. Treanda was another drug that
 was approved this year for B-cell lymphoma and ultimately what we would like
 to do is to develop an immunotherapy for T-cell lymphoma. We are working
 with some of the basic science groups at Yale to try to hook up various kinds
 of immune effector genes to targeting genes so that we can selectively get to
 those lymphomas cells and make the immune system work in our favor.Miller
 One of the things you talked about was called HDAC, or histone deacetylase
 inhibitors. On a very basic level, for me and for the listeners as well, can
 you explain what histones and deacetylase are?Foss Basically, if you look
 at our chromosomes, our genes are in chromosomes and23:51 into mp3file
http://www.yalecancercenter.org/podcast/Answers_Sept-21-08.mp3the chro-
 mosome consists not only of DNA, but also of proteins called histones that keep
 that wound up in a tight coil. We want that DNA to be wound up in a coil
 most of the time because coiling it up prevents the genes from being transcribed.
 We do not want our chromosomes making all kinds of genes all the time that we
 do not need, so the histones are kind of a protection to essentially silence some
 of those genes. We can modify those histones by acetylation and deacetylation,
 and that process basically allows them to fall off the DNA and allows it to open
 up so the genes can be transcribed. We know if we look at tumor cells versus

normal cells there is a different pattern of acetylation of those histones. If we actually treat tumor cells with these histone deacetylase inhibitors, or HDAC inhibitors, we can cause those histones to fall off the DNA and allow various genes to be transcribed, and some of those genes are genes that are going to turn off the tumor cell. This is an important process that we only recently learned about and I view this as a biological therapy because we are modifying proteins that are responsible for gene transcription in the cells. Miller I am going to ask you to make long-term predictions. What do you see in oncology, 20-50 years from now? Will these diseases be treated with chemotherapy as we know it now, or do you think there will be more of these biologic approaches? Foss The field is really moving toward biological approaches and targeted therapies. If you think about chemotherapies, by and large, they kill all dividing cells, they are not specific. We have learned from years and years of giving chemotherapy that is very difficult to cure more patients this way. We can put patients in remission, but do we really cure more patients? There was recently a summit where this was discussed on national TV, and a Newsweek article followed up. The point that was made in that article is that going down the same road with more chemotherapies that look the same, is not really going to help us. Most people feel that the future is in some of these novel agents like antibodies, like the HDAC inhibitors, and some of these other new targeted therapies that are targeting specific proteins or enzymes that we know are important for tumor cells. Miller I read that Newsweek article as well and you know what, it was sort of sobering and solemn in a way. You are experienced with treating non-Hodgkin lymphoma, do you feel pessimistic about it or more optimistic? Where have we been and where we are going? Foss I have been treating non-Hodgkin lymphoma now for almost 20 years. I started out at the National Cancer Institute when we thought that giving more chemotherapy was better. We have evolved considerably from that point and 26:45 into mp3file http://www.yalecancercenter.org/podcast/Answers_Sept-21-08.mp3 now what we are doing is taking a more holistic approach to the whole disease. We are looking at patients, and even if we know that we may not be curing those patients, we have very good drugs and very good strategies to keep their disease in remission and improve their quality of life. That is one major direction that we are going in. Another direction is focusing more on immunotherapies and thinking more about transplant and other immunotherapy approaches for patients. Even though the initial vaccine studies with B-cell lymphoma did not prove to be successful, I think we learned a lot about giving vaccine therapy. The next set of studies is hopefully going in a different direction and will allow us to use immunotherapy more broadly. I feel very, very optimistic about the future. Miller I have to say, listening to you, I feel the same way. As we wrap it up, what is available for patients in terms of support groups at Yale and other programs in the community? Foss Yale has a number of support groups for patients. We have lots of information available through our cancer line where patients can get information about diseases, how to obtain a second opinion, and also how to participate in our support groups. Specifically for lymphoma and leukemia patients, there are a couple of resources that you

should know about. The Leukemia and Lymphoma Foundation has a website and a Connecticut office, and the Lymphoma Foundation does as well. It is important to use these resources. Miller Thank you Francine. This has been a wonderful session. Thanks for being with me. For now, I would like to wish all of you a safe and healthy week. If you have question for the doctors or would like to share your comments, go to www.yalecancercenter.org, where you can also subscribe to our podcast and find written transcripts of past programs. Next week Ken Miller speaks with Lucinda Hogarty, the program director for the Connecticut Cancer Partnership. I am Bruce Barber, and you are listening to the WNPR Health Forum from Connecticut Public Radio.