

Dr. Thomas Lynch, Jr., Lung Cancer Awareness 2009 November 1, 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 Dr. Foss is a Professor of Medical Oncology and Dermatology specializing in the treatment of lymphomas. If you would like to join the conversation, 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. Thomas Lynch. Dr. Lynch is the physician-in-chief of Smilow Cancer Hospital at Yale-New Haven and he is an internationally recognized expert in the treatment of lung cancer.

Chu What got you interested in focusing your career on the treatment of lung cancer?

Lynch I actually got into lung cancer sort of by serendipity. I wish I could tell you that it was a well thought out decision in advance, but I was finishing my first year fellowship and I was looking at the numbers, and I saw that lung cancer, and this was back in 1989, that lung cancer was by far the leading cause of cancer death in the United States among men and among women. At the time, if you looked at the fields that people were going into, there was no one going into lung cancer, and I struggled and wondered why was no one going into lung cancer work at that point, and thought this was an area that needed a lot of attention and that is truly what drew me into it. As I got more interested in it, I realized that it was a field that had enormous potential for making an impact in terms of reducing the burden from cancer death.

Foss At the time that you were interested in lung cancer, back then, there really were very few treatments, if any, for the disease.

Lynch There were very few treatments Francine. Basically, in 1989 we gave platinum based chemotherapy. We saw modest improvements in terms of survival and we had not appreciated the full spectrum of how we could help patients with earlier disease, or even the advent of targeted therapies of lung cancer.

Chu Tom, to help our listeners understand and appreciate the magnitude of the problem, how many patients per year are diagnosed with lung cancer and how many people unfortunately will die from the disease?

Lynch There are some interesting statistics if you look at the American Cancer Society website. The number of people who are estimated to get lung cancer in the United States in 2009 is about 185,000, and the vast majority of those people will get non-small cell lung cancer. There are two major types, small cell and non-small cell, and non-small cell accounts for about 85% of the 185,000 cases. Now, the difficult thing about lung cancer is if you look at the overall five-year cure rate of lung cancer its only 15%. So, of those 185,000 people who get lung cancer in 2009, only 15% will be alive without disease in five years and that means the total 2:54 into mp3 file <http://www.yalecancercenter.org/podcast/nov0109-lung-cancer-awareness.mp3> death toll from lung cancer is in excess of about 160,000 deaths, which is more than colon cancer, pancreas cancer, and breast cancer combined. It is an enormous public health burden and yet, Ed, when you look at the spending on research, despite 180,000 cases and 160,000 deaths, when you look at the expenditures for research for lung cancer, we spend about \$1400 in federal money for each lung cancer patient who dies and yet we spend about \$14,000 for each prostate cancer patient who dies. You can see there is

a big difference in how we decide to allocate resources. Chu I am just curious Tom, why do you think there is such a huge difference between what's spent, what's focused on lung cancer, as opposed to prostate cancer? And I suspect the amount that's spent on breast cancer may also be much higher than that for lung cancer. Lynch Prostate and breast are the two highest that we spend on. Prostate happens to be the highest right now, but it used to be breast. Prostate and breast will change year by year based on the spending numbers, and colon cancer is some place in the middle. I think the biggest reason is probably that it's a smoking-related disease, and I think that a lot of people can look at things and realize that if we were able to eliminate smoking in our society, we would eliminate about 82% of all the lung cancers; somewhere between 10% and 20%, some might say as high as 20% others as low as 10 depending upon where in the country you are, say it's a disease that is not smoking related; the vast majority is smoking related. When you take a disease that's smoking related, a lot of the population feels like, 'well they smoked, that's something that they can control, why should we put money and resources into something that is largely a preventable illness?' Foss Can you talk about other causes of lung cancer that are not preventable? For instance, I know that there is passive smoke exposure and we talk about radon exposure and other things in the environment. Lynch There are other causes that are not directly related, so non-direct cigarette smoke, or secondhand smoke, probably accounts for some amount of lung cancer. Radon and asbestos probably account for some lung cancer. But I would argue that for the people who are never smokers that get lung cancer, it's still an unknown etiology as to exactly why they get lung cancer. What we have learned a lot in the past five to seven years are the types of lung cancer they get in terms of genetics of lung cancer, what we don't know is why did they get those genetic changes? But we have been able to profile molecularly what non-smokers lung cancer looks like. We still don't know what causes non-smokers to get lung cancer, which is a different question. 5:35 into mp3 file <http://www.yalecancercenter.org/podcast/nov0109-lung-cancer-awareness.mp3> Foss Is there an increase in the instance of lung cancer over the last ten years? The reason I am asking this is that I know there is an increase in non-Hodgkin's lymphoma that's probably associated with environmental factors, and I am just wondering with lung cancer have you seen that as well? Lynch The good news about lung cancer is that the overall numbers for men have come down very nicely, correlating very closely with the reduction in cigarette smoking since about 1970; we have reduced our amount of cigarette smoking. So, the incidence and cases in men have definitely gone down, and the number of cases of women has hit a plateau and are beginning, we hope, to come down as well, because women lag a little bit behind men in terms of quitting smoking and haven't quit smoking quite as quickly as men did, principally because there weren't as many women that smoked as men that smoked. I think that if you look at the overall numbers, the numbers are actually down from their peak. The peak was in 1992 for total number of lung cancer cases and it is now less than at that point, principally because we have stopped smoking. We are seeing more lung cancer in never smokers, but again it's a small number, so

it's hard to know if that's a true trend or just the way we categorize cases. Chu If an individual has stopped smoking, does the risk of developing lung cancer go back to say a situation where that person had never smoked before? Lynch It doesn't go back to the risk of a never smoker, but Ed, one of the most important things you point out is that if you stop smoking, the day you stop smoking, two things happen; your cardiac risk goes down and your lung cancer risk begins to go down. Now we know that within about a year to 18 months, the cardiac risk, the risk of having a heart attack or stroke, goes down to a rate similar to someone who doesn't smoke. That is an enormous reason, and that's even if you are in your 70s or 80s, to stop smoking even in that age group. For cancer, we know that when you stop smoking you begin to reduce your risk, but it takes many years for that risk to approach that of a never smoker. I think the biggest reason to stop if you are older is the combination of cancer and cardiac; if you are younger, cancer and cardiac risk. Foss Does it matter how early you start smoking? What we are hearing now is that there are more teenagers smoking. Are they going to be at greater risk because they started younger? Lynch There will be greater risk if their total number of packs a year is higher, and if you start younger, you have more time to be exposed. So, I think you are right. The other issue about people who are starting younger is it's clearly the biggest area of growth in tobacco use, are people who are in their early teens, and I believe that becomes a concerning trend for what the future might hold for lung cancer incidence. 8:19 into mp3 file <http://www.yalecancercenter.org/podcast/nov0109-lung-cancer-awareness.mp3> Chu In general, what age group is at the greatest risk for developing lung cancer? Lynch Lung cancer, like many solid epithelial malignancies, or solid tumors, things like colon cancer, prostate cancer, and breast cancer, tends to be a disease of people who are over 60 years; the typical age for a lung cancer patient. The average in the United States is now about 68 or 69 years old, that means that half the people who get the disease are under that age group, and there are still a substantial number of people who get lung cancer who are under 45, and there are probably 5000 to 10,000 Americans each year who get lung cancer who are under 45, but the majority of people who get the disease are over 60. Foss There is a lot of talk about screening in other kinds of cancers. Screening is now the buzzword to try to pick up cancers earlier. Can you talk about screening in lung cancer? Lynch Its a great point in terms of, do we have techniques in lung cancer that mirror what we can do in breast cancer, for example, or colon cancer where mammograms and colonoscopies have been shown to dramatically save lives? In lung cancer, we just don't have that kind of test yet. There is a lot of interest in using CAT scans, screening CAT scans, to try to pick up lung cancers early and while I agree this is a very promising technique, it's certainly not proven yet to be something that actually can reduce somebody's risk of developing lung cancer. The data just is not there. Yet, we have not done the large studies to evaluate CT screening and its ability to pick up lung cancers, or lesions that are small enough. What we know is that when you do chest x-rays, chest x-rays are not specific enough, and by the time the chest x-rays pick up a lung cancer, it's usually too late, the cancer has usually spread. Chest x-rays were not efficacious as a screening technique. The hope is

that perhaps CT scans might get better. I would argue that the long term hope for screening is that perhaps we will develop molecular screening tests where we can look at sputum samples and look for early changes in sputum that might predict for developing lung cancer; sputum being the secretions from the lung itself that might actually predict who is going to get lung cancer. It might be a better way to identify those patients who have early stage disease. Foss So at this point there is no blood test to detect lung cancer? Lynch There is not a blood test to detect lung cancer, but again, I hold that hope that we may see something like that down the road. There is some very interesting work that's being done at the intersection between biology and engineering looking at the development of specialized microchips that can detect small numbers of circulating tumor cells. A group that I used to work with at the Mass General Hospital in Boston has developed a small chip that can isolate one cell in approximately 2 mL of blood, which is amazing sensitivity, and so some people11:11 into mp3 file <http://www.yalecancercenter.org/podcast/nov0109-lung-cancer-awareness.mp3> are hoping that we may be able to use that as a potential screening test for cancers down the road, but it is many years away. Chu So presently the state-of-the art in 2009 is that we still rely on the clinical presentation? Lynch We rely on the clinical presentation and an aggressive effort to encourage people to stop smoking, but in terms of symptoms, we rely on internists, pulmonologists, and family practitioners recognizing that any smoker who comes in with cough or shortness of breath should be worked up appropriately and make sure that lung cancer is not part of what's going on. Chu How about in a non-smoker? Would they be the same symptoms that you would look out for? Lynch In a non-smoker symptoms will be cough, shortness of breath, any kind of blood tinge, if there is any blood in the phlegm that people cough, that sort of thing would be something that would make me concerned even in a non-smoker and you want to get a chest x-ray and make sure that there is no evidence of a lesion. Getting back to Francine's point, while I am saying that there is no screening test, that chest x-rays don't work for screening, chest x-rays are effective for evaluating people who come in with symptoms, because they can often show pneumonia or something that would make you think this isn't a lung cancer. Foss Once the patient has a suspicious lesion, a cough, or a symptom, the next step would be to try to get a biopsy, I presume? Lynch The first thing we do once we see something we are concerned about, we get a PET CT scan and a PET CT scan would look at the entire chest and belly, that's the CAT scan part of it, and the PET scan element would allow us to tell what the likelihood of a lesion being cancerous is. Once that's done, getting a biopsy becomes the next important step. There are several ways of getting a biopsy in lung cancer, sometimes you go to a pulmonary doctor who can put a scope down the airway, which is called a bronchoscope, and then he can put the scope down the airway itself and get washings from inside the lung. The second way of doing the biopsy is a radiologist using a very small, very thin needle from outside the chest and putting that needle directly into the spot of concern and aspirate a sample and look at that under the microscope. Foss This has been really interesting talking about lung cancer and I would like to talk more about the

treatment of lung cancer when we come back from the break. You are listening to Yale13:26 into mp3 file <http://www.yalecancercenter.org/podcast/nov0109-lung-cancer-awareness.mp3>Cancer Center Answers and we are here with Dr. Thomas Lynch discussing the treatment of lung cancer.Foss Welcome back to Yale Cancer Center Answers. This is Dr. Francine Foss and I am joined by my co-host Dr. Ed Chu and Dr. Thomas Lynch, Director of Yale Cancer Center and physician-in-chief of the Smilow Cancer Hospital at Yale-New Haven. Tom, we talked a little bit about diagnosis and screening for lung cancer, could you talk a little bit about the therapeutic approach for the disease?Lynch While there have not been as many advances in screening for lung cancer as we might like, there have been some recent advances in some of the diagnostic methods and some of the new treatments that we have for lung cancer. Probably the biggest thing that has happened in the past five to seven years has been a greater understanding of the biology of lung cancer. We now know that lung cancer is not just one disease, and what we have learned is that there are a number of important genes that are abnormal in certain types of lung cancer. Now, if you look at all the people who get lung cancer, as I mentioned earlier, about 85% of them have something called non-small cell lung cancer, and of all the people who have non-small cell lung cancer about 70% have something called adenocarcinoma. We now know if you look at adenocarcinoma of the lung, there are probably about 130,000 cases of adenocarcinoma of the lung a year in the United States. If you look at adenocarcinoma of the lung, we now have approximately six different mutations that allow us to guide treatment and therapy decisions and have allowed us to bring specific therapies. In two of those cases patient's who have something called EGFR mutations, and people that have something called EML4- ALK translocations, it looks like we may have effective therapies that can slow the growth of cancer, perhaps not cure patients, but certainly give them many extra years of life.16:10 into mp3 file <http://www.yalecancercenter.org/podcast/nov0109-lung-cancer-awareness.mp3>Chu

It should be noted to the listeners out there that Tom, your group when you were up in Boston at Mass General really were the leaders in identifying mutations in this epidermal growth factor receptor to show that, in fact, patients with mutations in that receptor could respond to a novel small target therapy.Lynch Ed, that's correct and I think one of the things that was interesting about that experience, and important for your listeners, is that that observation was made from working with patients who are having extraordinary responses to experimental or new therapies. I would encourage listeners to consider, if they are diagnosed with cancer, be it lung cancer, colon cancer, lymphoma, whatever disease it happens to be, to look at clinical trials as an option. That kind of breakthrough was made because patients participated in clinical trials and we saw these dramatic responses, and were able to investigate what might be causing, or responsible for, those dramatic responses. It wouldn't have happened if it weren't for patients participating in new clinical studies.Foss Are these new targeted therapies used in combination with chemotherapy, or are they used by themselves?Lynch That's a great question, and it's something that is evolving right now. The

tools that I talked about, the anti-EGFR and the anti-ALK therapies, are used by themselves, but other targeted therapies like the drug bevacizumab, which targets VEGF, an important molecule that determines blood vessel growth in lung cancers, is used with chemotherapy. I also hold out on the consideration that someday we may use these other drugs with chemotherapy. I think we just don't know that yet, it's something that is still in evolution. Chu Tom, we hear a lot about individualized/personalized medicine and that's kind of the buzzword in all the fields of oncology, but clearly it sounds like we have made significant advances in being able to individually tailor at least some therapies for patients with lung cancer. Lynch That's completely correct, and one of the things we are doing at Yale is we are building a facility for doing molecular profiling. If the patient comes in with a tumor in let's say the left upper lobe of the lung, we would do a biopsy of that tumor, get a sample of the tissue, and send a portion of that sample to the molecular profiling laboratory, and there we would look at all the possible mutations that we could detect to try to find a mutation that might help guide therapy in that setting. That's a real difference and a real advance over how we treated lung cancer just four to five years ago when we weren't doing that. I mean, if you look at your own field of colorectal cancer and think about how molecular profiling has advanced to help patients in that field, I think it's something that we are going to be seeing across the board of cancers. And Francine, the lymphoma molecular profiling has made an enormous difference in terms of how patients have done. I think this is going to be something we are going to see as a trend and a theme across cancers. It's something we hope to be doing at Yale, probably in the early part of 2010. Foss For our listeners, can we talk a little bit about how we do this whole process? We need tissue, and is that fresh tissue or could we get archived tissue? Say if a patient had a biopsy some place else and they wanted to come to Yale Cancer Center for this molecular profiling, how would that work? Lynch Often we can use what's called formalin-fixed tissue. So, if you have a biopsy done at an outside hospital and they have a sample of the tissue, what they do is take the tissue and they embed it in a wax substance, which makes it easier for the pathologist to be able to make very thin cuts of it and put them on a slide and look at it. That's the way they store tissue, they store it in these little wax blocks, and so if you have a wax block, or a paraffin block, you are able to sample that and often we can get the answer that way, but Francine, I think one of the differences between lung cancer and other diseases like colon and breast, is few patients have enough sample. Only about 30% of patients will have enough sample from traditional means, and so we often will recommend a separate core biopsy to be able to obtain tissue, but even then we will put it into those same paraffin blocks to be able to obtain the information, but often in lung cancer it may require a second biopsy, and that's something that the patient has to talk to the doctor about in weighing the risks and benefits for a given patient as to whether or not it makes sense. Colon cancer patients, the majority of them have their colon tumor taken out, the majority of breast cancer patients have their breast tumor taken out, for a lot

of lung cancer patients, the cancer has already spread before they get to that point, and so we don't have as much tissue to be able to do these molecular tests on. Chu Lets go back to say an individual who presents with a suspicious mass, biopsies made, and a diagnosis of lung cancer is then made. Take us through the process, the evaluative process and the decision-making process in terms of surgery, radiation therapy, and chemotherapy. Lynch The first thing you do when you see somebody who has been diagnosed lung cancer, you want to ask, could this be cured by surgery? Because of the 15% of patients we cure, the big chunk of those patients are people who are able to get to surgery. There are two factors that determine whether somebody's lung cancer is operable, or someone we can take to surgery. The first is, has the cancer spread outside the lung? And for that, the PET CT is the best answer. PET CT, plus a test called the mediastinoscopy where we go down and biopsy some lymph nodes. So, the first assessment is, in a perfect world, could we take this out, or has the tumor already left the lung? If the tumor has already left the lung, chemotherapy becomes21:56 into mp3 file <http://www.yalecancercenter.org/podcast/nov0109-lung-cancer-awareness.mp3> the best way to treat it. If the tumor hasn't left the lung, then the second important question is does the person have enough lung reserve to tolerate having that portion of their lung removed? Now, unlike other cancers, the majority of people that get lung cancer smoke, and they don't have good lung reserve, so if you end up taking out a big portion of somebody's lung, either a lobe or two lobes or sometimes the entire lung, you may not leave that person with enough lung capacity to be able to breathe. This is why a multidisciplinary team of a surgeon, a pulmonary doctor, a medical oncologist, and a radiation doctor together are in the best position to decide if surgery is the right treatment for Mrs. Johnson or Mr. Johnson, and so that's a key decision that needs to be made upfront, and seeing more than one doctor can often be helpful. One of the things we are trying to do, as you know, at Yale is to make multidisciplinary care a feature of the new Smilow Cancer Center. So, the first decision is surgery or no surgery. Once the decision has been made not to do surgery, if that's the case, one would then consider if radiation would help, and then after that, the decision of would chemotherapy possibly help? The decisions for radiation are for tumors that are enlarged in the lung, but haven't left the chest, they might have left the lung, but they are still within the chest cavity, and that's where we might consider radiation. For all other types of lung cancer, which is about half, we would treat with chemotherapy or investigational/experimental therapies.Foss Should a patient with lung cancer consider going on a clinical trial at the very beginning when they are diagnosed?Lynch We would encourage as many patients as possible to consider clinical trials even very early. For example, we have a clinical trial that's a national trial available throughout the country and for our listeners in Connecticut, it is available at many hospitals in Connecticut, where after surgery you have a clinical trial, which is looking at a new drug in what is called the adjuvant therapy of cancer. We know that despite surgery being the way that most people are cured, many people still have cells left behind in other parts of the body, even after surgery, and so a number of hospitals in Connecticut and around the country are

looking at comparing using chemotherapy with or without a new targeted drug to see whether or not that might be a better way of preventing treatment. One thing people should understand is that these trials don't involve placebo or no treatment arms in these trials. You would be receiving active therapy on either arm of the trial. We are just comparing two trials and doctors honestly don't know if one arm is better than the other arm of a trial. Foss I think that's an important point that you just brought up Tom, which is that for many cancers, lung cancer being one of them, we don't as physicians really know what the right24:41 into mp3 file <http://www.yalecancercenter.org/podcast/nov0109-lung-cancer-awareness.mp3> treatments are for a lot of patients, and we still need these clinical trials in order to know what the best approaches are. Lynch Absolutely, and I think that if you look at the debate over health care reform, regardless of what position anyone takes on that debate or what side you are on in that debate, I think the one healthy thing that has come out is the recognition by republicans and democrats that we need to look more carefully at what we are providing in terms of health care, what the outcomes are, and whether or not we are giving the benefits to our patients that we need to be able to give. The only way we are going to do that is by doing clinical trials to be able to determine what the optimal therapies are. Chu What is remarkable, and I think the statistics hold, is that it has been estimated that perhaps less than 5% of all cancer patients in fact go on a clinical trial, which is really an astoundingly low number. Lynch An outstandingly low number, particularly because when you look at the outcomes for those patients who go on clinical trials, those patients do better than patients who do not go on clinical trials. So, it's something that we really are trying very-very hard to do, to be able to offer clinical trials to every patient who has a disease that we possibly can. Now there are a lot of reasons why it is difficult, the bureaucracy is ever expanding and the cost has gone up in terms of what it takes to do this, but at the major cancer centers there is an enormous commitment to providing clinical trials that are important, not only at the cancer centers, but also at very good community hospitals around the state where there is an effort to be able to provide clinical trials. Foss Are there any gene therapy trials now in lung cancer? Lynch Great question, there is actually a trial where people are trying to look at some gene based treatments such as some vaccine therapies. I wouldn't say there is anything that would be a traditional gene replacement strategy that's being looked at in lung cancer. There are some therapies where people are injecting genes into cells to try to create better vaccines, again highly experimental, and there are some other therapies where people are using what are called antisense oligonucleotides to turn genes on and off. I would consider both of those examples of gene therapy because they involve gene transfer, but again highly experimental and not something that I would say is right at the forefront of lung cancer research right now. Chu Tom, you have been very actively involved in developing new targeted therapies, what are some of the newer targets, newer agents that really excite you?27:10 into mp3 file <http://www.yalecancercenter.org/podcast/nov0109-lung-cancer-awareness.mp3> Lynch I was just at a meeting this past weekend in Philadelphia with a number of lung cancer doctors, and I think that

we all would agree that the thing that's the hottest this year is this EML4-ALK disease that was discovered. What's amazing about it, in 2007, which is only two years ago, a group in Japan discovered a new type of lung cancer where the gene that was abnormal was a translocation between the EML-4 gene and the ALK gene, which is something that Francine knows a lot about because it's the anaplastic lymphoma kinase gene seen principally in lymphoma before this and something that Francine has worked on, and so when they found these two genes were put together in never smokers, they ended up having lung cancer, and that was discovered in 2007. Just this year, at the American Society of Clinical Oncology Meetings, our group reported dramatic responses to a new drug for this group of patients. I actually had a patient of mine from New Hampshire who has had an amazing response that has lasted a year and a half of all of the cancer going away in that setting and there is a lot of enthusiasm on getting that into the main line and making sure that the patients who are never smokers are tested for this EML4-ALK gene translocation. Unfortunately, it hasn't been seen in smokers, it's only been seen in never smokers at this point. Foss That's very encouraging for people out there who have metastatic lung cancer and really aren't getting good news about their disease. It's exciting to hear that there are some future advances that are going to help patients. Chu Tom, it's amazing how quickly time has gone and in the 30 seconds that we have remaining, any take home messages for our listeners out there? Lynch I think the most important thing when you think about lung cancer, is to focus on the prevention aspect of it. We all know people who are loved ones in our lives, who continue to smoke, and if we can work together as families and as communities to try to help people do their best to stop smoking, that's probably the most important thing a community can do to be able to reduce the burden and death from lung cancer. Chu Great, as always it's great having you on the show and we look forward to having you on a future show to hear more about lung cancer and also about all the great advances that are taking place under your leadership at Yale Cancer Center. Lynch Thank you Ed, and Thank you Francine. Foss Thank you. Chu You have been listening to Yale Cancer Center Answers, and we would like to thank our 29:31 into mp3 file <http://www.yalecancercenter.org/podcast/nov0109-lung-cancer-awareness.mp3> guest Dr. Thomas Lynch 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 any questions or would like to share your comments, you can 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.