

Yale CANCER CENTER *answers*

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Study for Advanced Lung Cancer Patients

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Welcome to Yale Cancer Center Answers with your hosts doctors Francine Foss, Anees Chagpar and Steven Gore. Dr. Foss is a Professor of Medicine in the Section of Medical Oncology at Yale Cancer Center. Dr. Chagpar is Associate Professor of Surgical Oncology and Director of the Breast Center at Smilow Cancer Hospital and Dr. Gore is Director of Hematological Malignancies at Smilow. Yale Cancer Center Answers features weekly conversations about the research, diagnosis, and treatment of cancer and if you would like to join the conversation, you can submit questions and comments to canceranswers@yale.edu or you can leave a voicemail message at 888-234-4YCC. This week you will hear a conversation about clinical trials for advanced lung cancer with Dr. Roy Herbst. Dr. Herbst is Ensign Professor of Medicine and Professor of Pharmacology and also Chief of Medical Oncology at Yale Cancer Center and Smilow Cancer Hospital at Yale-New Haven. Here is Anees Chagpar.

Chagpar Why don't you start by telling us a little bit about what you do in the context of lung cancer at Yale Cancer Center and Smilow Cancer Hospital?

Herbst As you probably know, lung cancer is the number one cause of cancer death worldwide. So it is a major medical problem, and at Yale Cancer Center we look at ways that we can improve the outcomes for patients with lung cancer and one of the best ways to do that is to better understand the cancer through molecular profiling and looking at the different genes, different proteins, and different constituents of the tumor that causes it to grow, and also understand what is driving the tumor and then try to match the patient with the best clinical trial. We are doing this in a number of ways, right now we have well over a dozen trials that we are studying in lung cancer, for patients with all different stages and types of disease.

Chagpar You brought up a few concepts that I want to take individually. The first is this whole concept of molecular profiling and figuring out what genes, what constituents as you put it, drive these cancers. Are all cancers driven based on molecular abnormalities and genetic mutations or are there other factors at play as well? How do we figure out what really causes cancer to grow?

Herbst By definition, a cancer cell is abnormal. It is growing out of control. So yes, there is some reason why that cancer cell is growing. What we have learned over the course of the last 15 to 20 years is that all lung cancers are not the same. In fact, almost no two are exactly the same. And by that we know that the molecular drivers, the characteristics, the switches in the cell can be very different between patients. So, if we gave all patients the same therapy, let's say the same chemotherapy, it might have some effect, but in some it might be very effective and in some it might have no effect at all. So, what we really need to do is divide and subdivide patients, based on our understanding of what is causing that tumor to grow, into clinical studies that are most appropriate for that patient. One good example that we just started actually is a trial that I have a national leadership role in called the Lung MAP Trial, the lung master protocol. Let me tell you how it works. Let's say a patient has lung cancer, and this is for a very specific type of lung cancer, squamous cell lung cancer that is about 20% to 25% of the lung cancers, it tends to occur in people who have smoked, not always, but most people have smoked and these patients come in and they have cancer and they have already failed one chemotherapy treatment that might have been at a place in

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Connecticut or it might be in another state in the country. It might have been at Yale. So what we do is, we look at that patient and say, okay we need to now figure out what to do next. In the old days, what we would do is we would say, well here is a drug, we will try it, or we might say, here is a clinical trial, we will try that, but now we hopefully can do one step better. What we do is we actually take the tissue, the biopsy that the patient had, and if there is not enough tissue from that biopsy, we actually have resources within the trial to obtain a new biopsy, a new piece of tissue, and we then send that off and within 14 days we have analysis of over 250 different genes. Different processes in that cancer that may or may not be causing it to grow. Then, based on that, we sort that patient to one of five different drug trials. Basically what we are doing is we are finding the right drug for that patient at the right time and we are doing this at Yale, but it is actually also open at over 400 sites around the country. So, it is a national effort to try to match patients to the right drug. Now will this be more effective? We do not know yet. We assume that it will be based on what we know about molecular biology, but that is why we are doing the trials and we are trying to get these trials available throughout Connecticut. Patients are coming to Yale from other sites throughout the country, but the good thing is these trials are open at many sites around the country in community settings because we want to take the science, the understanding that we have generated, myself and my colleagues, and then translate that to as many patients as possible to help them benefit and get the most benefit from these agents.

Chagpar This is really what we talk about when we talk about personalized medicine, where we are looking at these genetic mutations, these molecular biology alterations, and trying to pick out what therapies might be best for them. When you look at these 400 mutations, these 400 genes, do we actually we have the drugs that will target each of these for these five clinical trials?

Herbst We do, and what we have done is we have entered into a public-private partnership. Groups and drug companies that make these drugs, have these compounds, in the case of this trial, four of them are oral agents, one is IV, and what we basically do is the drugs are made by the companies, but if they are going to try to do a trial without this mechanism that I am describing, it is very hard for them to enroll patients and the reason for that is many of these abnormalities occur in very small percentages. For example, one abnormality in something called FGFR, for those interested that is fibroblast growth factor receptor, occurs in perhaps 10% of patients with lung cancer. That means that 1 out of 10 people will have that abnormality and have the potential of benefit from that trial. And if we were doing that trial as a single trial at Yale, and we have tried that in the past, many people would come in and many would be disappointed, because they were not a candidate for the trial. So, the first thing that is a concern to me as a clinician is that we do not have something to offer our patients, but it is also quite unsatisfying from the clinical trial point of view as well, because we can't find the patients to go on the trial and of course the more people that are treated on the trials, if we find the drugs work, that gets them approved and available throughout the country. So, it is really not helping anyone. So, with this new mechanism that I mentioned, we profile the patient for a number of different genes and we picked five different drugs, five different pathways that we hope will include almost all the patients. So this way, if a patient does not get arm A, they can get arm B, C, or D, and so far it is working well. I actually just came off a call

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a little while ago and as many as 20 people are now enrolled nationwide. It has only been open for a couple of months and the numbers are climbing as word gets out there, and certainly programs like this are helping with that. And this is just one area where I think we are really using technology and getting that technology to impact on patient care and as you know Anees, there is often a lag between a new technology whether it be a surgical technology or a medical breakthrough and understanding how cells work, to translating that into benefit for the patients. I think one of the goals that we have here at Yale Cancer Center is to try to accelerate that, it is something we should be doing as a teaching hospital and one that is focused on cancer.

Chagpar And it certainly sounds like that is something that this is doing and trying to really figure out which drugs are the best for which patients and tailoring those, but I wonder why it is that you find that patients sometimes have some trepidation about being part of a clinical trial? It is great you are going to profile my tumor, why can't you just give me the drug that is best for me rather than enrolling me on a clinical trial? Do you ever get patients who ask you that?

Herbst Sure, and certainly I would want that for myself as well. You have a cancer, you are scared, you have a new diagnosis, and you want to get the drug that is most likely to work. The problem is that with many of these new therapies they are not proven to be of benefit yet and in some cases they may even have new side effects that one might not have with the standard of care. So as someone who is running the trials or is participating in the studies as a treating physician, you have a certain equipoise, you do not know is this drug better or not. You have to do the trial in order to figure it out. Trials come in different varieties, in the early stage and an area that I am very excited about right now at Yale is our Phase I Program. The earliest drugs that come out of testing from preclinical animal models are making it into the clinic, and we have a big push now to build our phase I program. We have Dr. Paul Eder and Dr. Patricia LoRusso, both within my section of medical oncology who are leading this effort. In these studies everyone gets the drug. The down side is it is quite early and in some cases we are still figuring out what the right dose or schedule is, how often to give the drug, but in those cases everyone gets the agent and it may benefit and it may not, and of course we do not do anything where we do not have a good scientific basis for doing it. Then there are phase II studies, which are larger cohorts. We have already tested the drug in the first patients so we have a little bit more information regarding its safety. There we are looking for activity, often in a specific subset of patients with specific abnormalities, and then there is the phase III trial, which I just described like the Lung MAP. I think that what we try to do is to find the best trial for any given patient, certainly if the patient qualifies for a trial, where they might get the study drug in a phase II, we offer it to them. One area of great interest right now is immunotherapy for lung cancer. Dr. Scott Gettinger in our clinic, along with our team, myself, and others, actually have a number of trials right now where we are looking at ways to enhance the body's own immune system against the tumor and we are quite excited about that. I think we probably have one of the biggest portfolios of drugs in this area in the region and we also are trying to look at the science behind how these drugs work, or more importantly, do not work, so we can figure out how more patients might benefit, and it is quite exciting. We now know that the

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immune system in many cancers cannot recognize the tumor, because the tumor creates a force field that keeps the immune cells from killing it and there are now therapies, many of them developed through technology that was pioneered by Dr. Lieping Chen, a scientist here at Yale, where we can actually use antibodies called PD1 or PDL1 and these antibodies are intravenous drugs, and we can break this force field on the tumors so the immune cells can attack it and we are seeing wonderful results, not in all patients, but in many. Again, it is another area that really is helping us to treat patients, learn how to treat even more patients in the future, and hopefully from the efforts of myself and the rest of the team, patients will go on to clinical trials so that the results will result in these drugs becoming available as a standard of care, and that is what we are really trying to do, we want to have the innovative approaches to these diseases, give patients a fresh look and then study these in very rigorous ways, of course with the patient's safety being a primary concern, and if the drugs do in fact pass the bar, then they become approved therapies for all to receive throughout the country.

Chagpar It sounds like certainly immunotherapies and targeted therapies are two of the hottest topics in cancer research now and it is a very exciting field. I think the real key point is what you said at the top of the show, which is historically we give patients chemotherapy as standard of care, but it does not really work for everybody. So in a sense what you are trying to do is develop tomorrow's therapies today and the way that people can help us to do that and to receive those therapies is by participating in those clinical trials.

Herbst Absolutely, but I also think it is important for people to realize that the clinical trials give them access to some of these new agents earlier and you know none of these immunotherapies that I mentioned are approved agents. The only way to get them is on clinical trials, and we still do not know the full spectrum of side effects associated with these agents and of course if you unleash the power of the immune system against the tumor, you might have some backlash against some of the normal cells from the body, but that said, we are talking about a disease like lung cancer where many of the people that I see have already failed therapy, they are coming from other places around Connecticut, New York, someplace else in the US, outside of the United States, looking for a fresh look, for new hope and of course understanding the risks, and improving benefits, clinical trials offer great promise and one thing that I feel very strongly about is at places like Yale University where we have great strength in basic science of cancer, but also in clinical care of patients, we want to try to match the two and that is what we call translational research and one of my roles at Yale is to promote that and the types of program that tell you about now really are in that direction.

Chagpar We are going to learn much more about translational medication and how we are really moving from the basic science to the bedside to improve patient care and lung cancer with my guest Dr. Roy Herbst right after we take a short break for medical minute, stay tuned.

Medical

Minute

The American Cancer Society estimates that in 2014, over 1500 people will be diagnosed with colorectal cancer in Connecticut and nearly 150,000 nationwide. When detected early, colorectal

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cancer is easily treated and highly curable and as a result it is recommended that men and women over the age of 50 have regular colonoscopies to screen for the disease. The patients with colorectal cancer have more hope than ever before due to increased access to advanced therapies and specialized care. Clinical trials are currently underway at federally designated comprehensive cancer centers like the one at Yale and at Smilow Cancer Hospital to test innovative new treatment for colorectal cancer. Tumor gene analysis has helped improve management of the disease by identifying the patients most likely to benefit from chemotherapy and newer targeted agents resulting in more patient specific treatments. This has been a medical minute brought to you as a public service by Yale Cancer Center and Smilow Cancer Hospital at Yale-New Haven. More information is available at yalecancercenter.org. You are listening to the WNPR Connecticut's Public Media Source for news and ideas.

Chagpar Welcome back to Yale Cancer Center Answers. This is Dr. Anees Chagpar and I am joined today by my guest Dr. Roy Herbst. We are talking about lung cancer. Now Roy, at the top of the show we spent a lot of time talking about various kinds of new therapies, immunotherapies, targeted therapies, some of the really cool things that you are doing to move this field forward. One of the things that was striking for me though was how prevalent lung cancer is and how many people it kills every year in this country. Can you talk about that in the context of the research that is being done? I mean, are we going to make any breakthroughs? Are we going to lower that mortality rate and if so, how?

Herbst I think the answer is, yes. We already see the impact we are making. Lung cancer is quite common, it affects almost 200,000 people a year in the United States. Worldwide there are probably close to 2 million people who die from it. It is just an incredibly prevalent disease, and what the main reason for that is of course the toxins which cause lung cancer. The primary one being smoking, though we are finding that only 80% of lung cancer patients now have a history of smoking, so it is a disease both of smokers, former smokers and never smokers. It is a little different in each of those cases but the key thing to lung cancer is to detect it early, one of the things we know is that lung cancer has a tendency to spread or metastasize so we do want to find it early and that is why people with significant smoking histories, over the age of 55, we recommended that they get screened with a CAT scan once a year. We do that here at Yale. I think that is important. Even when you find the lung cancers early, there still is a cancer that it can come back, but it is much less than if you wait and it occurs in a more advanced stage. So, that is very important. One thing that I have seen over the course of my career in the last 20 years are amazing advances in treating what we call locally advanced lung cancer, sometimes lung cancer occurs in a lung with a nodule or mass with lymph nodes present within the lung, it has already started to spread and when you combine different modalities, I am a medical oncologist so my modality is usually chemotherapy, but I work very closely with radiation oncologists who use radiation therapy to target the cancer and the lymph nodes and in many cases surgery is an option. So using those three modalities together, which can be done quite well at a place like Yale Cancer Center and Smilow Cancer Hospital where we can actually work as a team. This morning

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I was at a Tumor Board. We discussed all of our cases from last week and that is what is done at a care center like ours where we review the cases with all the different people present, surgeons and medical oncologists, radiation oncologists, the pulmonologists and the other caregivers, to try to bring a very coordinated effort regarding the care. So I think we are making a big impact there and I have seen that as well but the area where I think we are really having an amazing impact right now is in the advanced disease setting which are more than half the patients. More than half the patients with lung cancer present with disease that has already left the lung. So a surgeon like yourself, Anees, it would not help to cut it out because you are still dealing with cancer not only in the lung, but in the liver or in the adrenal glands or in a bone some place, so that is where we have to find a systemic therapy, something that goes into a vein or goes down the mouth as a pill and works throughout the body. And we now know that certain tumors, especially in those patients who have not smoked or have not smoked in many years, might have certain gene mutation, something called epidermal growth factor receptor and if we give the patient a certain drug the tumor can shrink in 80% of the cases with very little toxicity. It is still a small proportion of the patients and sometimes they become resistant so we have to treat them again with a new agent but that is great progress that we have seen in this disease and there are two or three other mutations, one we call ALK, also something called RAS-1. So for about 15% to 20% of the patients we have these new therapies where we can give an oral agent and we see wonderful results. What I wake up each day worrying about are the other 80%, what do we do for those patients other than taking the tumor to Yale's West Campus, right on 95, exit 42, and you sequence the tumor and you do not find anything that you can match to the right drug. For those patients, we have got to be even more creative. We have got to say, okay, maybe we need a combination of drugs. We need a clinical trial where we know that a certain pathway, for example, one is called KRAS and it occurs in 25% of patients with adenocarcinoma of the lung, a type of lung cancer, we know that we can't target that directly yet, though we are trying but maybe we can target two or three pathways downstream, meaning we know what this is the concert master that turns on two or three different processes within the cell, maybe we can combine a few drugs together and we are doing that. We do that and the trial we call the BATTLE trial. We have a combination of drugs that targets KRAS or as I told you earlier, immunotherapy. In many of these patients we know that the cancer has mutations. The immune system should be all over this cancer but we also know the tumor has adapted and figured out how to protect itself from this. Well in that case we have to block that immune check point and we have drugs and trials to do that in our lung clinic right now, Dr. Scott Gettinger and myself, Dr. Sarah Goldberg, the three of us have several trials between us that are using different agents, different combination of agents to activate the immune system against cancer and we do not stop there though. We take the tissue from these patients either before they are treated or after they are treated and we work with our laboratory sciences as you can only do at a place like Yale at a big teaching Hospital where we have a cancer center with all those resources and we are figuring out in those who respond and do well, why, and in those who do not, how can we do better? How can we combine things together? So this is the promise of lung cancer. It is a very devastating disease but we are trying to find new things to offer hope to patients, figure out the right way to treat each patient in a personalized way, and of course, do as best we can to prevent it whenever we can and for that we have a very strong smoking cessation clinic, for

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example, where we work with the patients, if we treat them for their cancer and then they are still smoking, we try to prevent them from smoking anymore and Dr. Ben Toll and others in our group are very actively involved in that.

Chagpar It certainly sounds like you are doing a lot but there are a couple of points that I picked up on and I would bet some of our listeners might be thinking about too. The first is that you said that there is a good proportion of people now who get lung cancer, who never smoked, and the second thing is that you know the best thing to do in terms of finding cancer earlier is to get screened, but the people who are getting screened are heavy smokers over the age of 50. So if you are sitting on the couch and it is Sunday evening and you are listening to Yale Cancer Center Answers and you have never smoked, and you are thinking my goodness, I still have a potential to get lung cancer, you just told me that a lot of the lung cancers present late when there are fewer therapies available and it is more challenging, what do those patients do? Should they get screened and if so how, if not then what do they do? Do they feel like they are a ticking time bomb that they may get lung cancer, should people go and get some sort of genetic testing to see whether they are genetically predisposed to get lung cancer, how does that work?

Herbst Those are many questions, let me take one at a time. For the person who is currently smoking and if they are over 55, I probably would suggest they get screened. The first thing of course I would like them to do is to stop smoking. I recognize how difficult that is, I actually chair a subcommittee on tobacco and cancer for the American Association for Cancer Research and we actually know that 18% of Americans still smoke. Now, if you look at the 50% or more that smoked 50 years ago before the first Surgeon General's report that is great. It is still 18%, which is a lot of Americans. So we need to work with people whether it be with behavioral methods, with medications, to help them to stop smoking and of course as they do that we want to screen them in case they have developed a nodule and screening has been shown to save lives so that is one thing that we definitely want to do. Now for those people who have never smoked, and that is good, do not start, there are other ways to be exposed to the toxins that can cause lung cancer whether it be environmental, whether you live in New York or Montana, you have different exposure in the air and it might be that you are exposed to radon which is quite common around here unfortunately, asbestos, many of the old structures here have asbestos as well, those can also cause lung cancer or it might be that it is a genetic cause, we do not really yet know too much about the genetics and there are some families with predispositions to lung cancer, we have not completely figured out how that works. We do know that if someone has not smoked, they tend to be more prone to get this epidermal growth factor receptor driven lung cancer, the only good news there is that it seems to be a bit more treatable than the standard lung cancer but again, we are learning each day and that is why we profile patients, we understand what is driving the tumor and try to match the right drugs to each patient. But it is a common disease and it really does need a very close analysis of the tissue and the tumor type and also the staging and how to treat it, either simply with medication, chemotherapy or targeted therapies or in many cases you want to use surgery or radiation therapy and that is the type of thing that we can help with in our clinic.

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- Chagpar So, if you have never smoked, you are not a candidate for screening with CT scan right?
- Herbst At this time the guidelines would say no, normally it is people that have what we call 30-pack years of smoking history, meaning you smoked one pack a day for 30 years or two packs a day for 15 years and/or any combination thereof, but there are no absolutes here. I think a discussion with your physician based on your relative working history, based on your family history is all quite reasonable, but clearly the best way to deal with lung cancer is to prevent it and primary prevention is important but sometimes it occurs and you cannot find any known cause, which is unfortunately the case in many cancers.
- Chagpar But one thing that you can do is you can be cognizant of the symptoms of early lung cancers and make sure that you seek appropriate medical care. Can you talk about how lung cancer might present before it becomes widely metastatic?
- Herbst What I see, and I have been doing this for quite some time, is typically what you see is someone who has had some sort of chest symptoms whether it be cough or shortness of breath. Many times they believe they have pneumonia which does not get better after several courses of antibiotics and normally then the primary caregiver will check the chest x-ray or CT scan, not quite as often, but more often than I would like to see, patients present with the cancer already metastatic, meaning they might be having symptoms of fatigue or bone pain because the cancer has gone to a bone, there might be central nervous systems symptoms because the cancer has invaded their brain or they might have issues with their liver . That happens in some cases as well but really the most common things are cough, sometimes the cough will have some blood-tinged sputum, meaning you bring up a little bit of blood, but again, very often lung cancers are diagnosed incidentally. Just in the last week I know of one cancer where someone went in for a GU procedure and the CAT scan happened to pick something up in the bottom of the lung and in another case, someone trips and they end up in the emergency room. They get an x-ray. And those patients are actually quite lucky, because we are finding it early. Wouldn't it be great if some day we could find it with a blood test or now even with breath, breath condensation from when you breathe, people can pick up early signs of lung cancer. There are some studies now, where there are certain dogs that can smell the early signs of lung cancer. All these types of things are being discussed and you see these at meetings and in the literature, we have got to find even earlier detection methods to find that someone has this abnormality because clearly we know that once the cancer has spread and metastasized it becomes much more difficult to treat.

Dr. Roy Herbst is Ensign Professor of Medicine and Professor of Pharmacology and also chief of Medical Oncology at Yale Cancer Center and Smilow Cancer Hospital at Yale-New Haven. We invite you to share your questions and comments, you can send them to canceranswers@yale.edu or you can leave a voice mail message at 888-234-4YCC. As an additional resource, archived programs are available in both audio and written format at yalecancercenter.org. I am Bruce Barber hoping you will join us again next Sunday evening at 6:00 for another addition of Yale Cancer Center Answers here on WNPR Connecticut's Public Media Source for news and ideas.