

Yale CANCER CENTER *answers*

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Targeted Therapies for Lung Cancer

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Welcome to Yale Cancer Center Answers with your hosts doctors Anees Chagpar, Susan Higgins and Steven Gore. Dr. Chagpar is Associate Professor of Surgical Oncology and Director of the Breast Center at Smilow Cancer Hospital at Yale-New Haven. Dr. Higgins is Professor of Therapeutic Radiology and of Obstetrics, Gynecology and Reproductive Sciences and Dr. Gore is Director of Hematological Malignancies at Smilow and an expert in Myelodysplastic Syndromes. 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 it is a conversation about targeted therapies for lung cancer with Dr. Scott Gettinger. Dr. Gettinger is Associate Professor of Medicine and Medical Oncology at Yale School of Medicine and here is Dr. Steven Gore.

- Gore So lung cancer is pretty common. It seems to me when I was in Maryland, it was a huge state for lung cancer and I think lung cancer was probably the most prevalent cancer in Maryland. Is that true up here as well?
- Gettinger Lung cancer is not the most common cancer. In men it would be prostate cancer and in women it would be breast cancer, but it is the most common cancer related cause of death, so if you add up all the deaths from colon cancer, breast cancer, prostate cancer, they do not equal the number of deaths from lung cancer in a year, despite there being many more of those cancers.
- Gore All of those put together?
- Gettinger Yeah.
- Gore And that is because in part prostate cancer for many people is an incidental finding right, and it often does not need treatment or minimal cancer treatment?
- Gettinger I think that is part of it. The other part is that lung cancers are often diagnosed at a later stage when it is not curative.
- Gore And why is that? Why don't we find out about lung cancer earlier?
- Gettinger Because we did not have active screening programs up until recently and by the time you develop symptoms from lung cancer, it is often already metastasized.
- Gore And certainly some people should know that they are at reasonable risk for lung cancer, I mean if they are heavy smokers and people probably by now have seen the black box warning on the cigarette box?

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- Gettinger I think so.
- Gore So shouldn't those people be checking in every three months and scanning themselves or something?
- Gettinger We struggled with that for the last 20-30 years and there were some trials, but none of the trials were really positive looking at x-rays versus doing nothing and finally one trial did show a survival benefit of screening with PET scans in patients who are at high risk for developing lung cancer, patients who have smoked heavily and smoked within the last 15 years.
- Gore So how often do we recommend that currently?
- Gettinger Annually.
- Gore Annual CT scans?
- Gettinger And it is a low resolution, low dose radiation scan and at Yale there is an active program to try to understand the findings on these CAT scans because often you will see little things that are meaningless.
- Gore Little ditzels.
- Gettinger Yeah that is a good word.
- Gore And so what happens when you find a ditzel?
- Gettinger We have different algorithms as what we should do, should we just follow this, should we biopsy it and there is also a lot of anxiety as you can imagine from a patient when you are told that you have a shadow in your chest and most likely it is going to be benign, but you have to deal with that anxiety.
- Gore That shadow thing, it is like saying you have a euphemism in your chest.
- Gettinger Exactly.
- Gore Susan, shouldn't we be worried about irradiating all these people with this CT scan stuff?

Higgins In general as Scott was noting, these are very low level types of exposures and when they did these studies, they were thinking about the fact that there is going to be some exposure but it is always a risk-benefit and for certain high risk subsets, my understanding is that the risk-benefit is much more on the side of benefit because they can potentially get early detection.

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Gore Scott, who should be considered for this?

Gettinger Generally, if you have what we call a 30-pack-year history, so that is the number of cigarettes that you smoke a day times the amount of years you were smoking, so if you have smoked one pack of cigarettes a day for 10 years, you would have a 10-pack-year history; the recommendations currently are if you have a 30-pack-year history and you are either currently smoking or quit within the last 15 years, you should have annual CAT scans.

Gore What about the people who quit prior to 15 years? Are they at no increased risk of lung cancer compared to healthy people who did not smoke?

Gettinger They are at increased risk but the risk goes down after that 15 years and then that is the risk-benefit toxicity profile.

Gore So they just have to hope for the best?

Gettinger Yeah.

Gore Let's have you walk us through this, so I am in the screening program, hopefully I have given up smoking by now because my internist put the fear of higher power or cancer or something, in me, I drank the Kool-Aid and I am getting these scans and I am okay and then my internist finds, let us say something more than a ditzel, something that is a nodule or a worry, what is going to happen next?

Gettinger Let's say you have your first scan and you see a 2 cm lung nodule that has spiculated edges, so it is not completely round, it has got little edges to it which is very worrisome for malignancy, at that point, you will have further work up done and depending on our

different algorithms, that might just be a biopsy and then a surgery or it might be additional imaging like a PET scan, or might be invasive staging like mediastinoscopy.

Gore That is a long word Scott, I do not even know what that is.

Gettinger It is just the sampling of the area in between your lungs that hold lymph nodes, so when you find a nodule like that, ideally you will be seeing a pulmonologist who will be interpreting these films for you and can take you through this and if you find something, your pulmonologist will say, this is the next step and the next step often is a biopsy or another scan.

Gore So, how do you do the biopsy in the chest, do you have to open up the chest?

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Gettinger No, you generally use either a CAT scan or in some situations an ultrasound to visualize the lesion and then you insert a needle into that lesion.

Gore Through the chest?

Gettinger Through the chest. For example, if you have a patient lying on a table and you have a CAT scan going, you can see a lesion exactly and you put a needle into it and you can see the needle go into it. The other way to sometimes biopsy is with a bronchoscopy where it is an outpatient procedure, you lie down on a bed and a pulmonologist inserts a tube into your lungs with a little camera.

Gore Through my throat?

Gettinger Through your throat and they can find where the lesion is and they can biopsy it.

Gore I am not awake during that right?

Gettinger Depending on the pulmonologist, some put you down a little bit more than others.

Gore I want to be down. Are these tests pretty reliable, if they tell me that this is benign, can I believe that?

Gettinger Good question, because if the concern is so high, even a negative biopsy does not exclude a malignancy, so in some situations where it is very clear that this is going to

be a lung cancer, you do not necessarily even need a biopsy, you can just go and do the surgery because a negative biopsy does not mean necessarily negative, it may be that you just biopsied an area where there were not any tumor cells or you just missed it in a sense, so there are certain characteristics on an imaging study that would lead someone to a suspicion for lung cancer or not.

Gore And part of this is, as you said, is kind of spiculated?

Gettinger Yes, if you have little spines on the surface of the nodule and there is another type of finding which is quite common and we call it ground glass, it is a little haze in the lung and that is somewhat troubling because those are often precursor lesions to cancer and we follow those and we do not take those out. If they get big enough or if they become solid appearing rather than the haziness, then that would lead us to do something to further evaluate.

Gore But a round nodule is okay?

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Gettinger Even a round nodule can represent a cancer if it is very well circumscribed, it could be other things, other benign type of nodules.

Gore I see, so no nodule should be ignored.

Gettinger If you see one, you are either going to follow it with another scan or you are going to act on it, meaning a biopsy or some type of surgery or a further imaging study.

Gore So you have put some needle into me and you have given me bad news that it looks like cancer, the positive diagnosis of cancer is reliable I assume, you are not going to tell me it is cancer and make a mistake? The pathologists are pretty careful about that, I am guessing?

Gettinger Yes, they take it very seriously, so it is more likely you will get a false negative than a false positive.

Gore So you have heard that you have got the big C, so what is next?

- Gettinger Staging would be next and depending on the characteristics, staging can include things like PET scans.
- Gore Staging means what, seeing where else it might be or how far along it is?
- Gettinger Exactly, we want to see if it is anywhere outside of the lung. We also want to see if it is in the lung, in the lymph nodes within the lung and outside of that nodule and in lymph nodes in between both lungs, an area that we call the mediastinum.
- Gore And that is the one you scan you said.
- Gettinger Well you can do that with scans and then there is staging where you actually put a camera behind the sternum and you are able to sample the lymph nodes there if there is enough suspicion and concern that those could be involved with cancer.
- Gore And you do this all before you do surgery on the lung?
- Gettinger Generally, we do this before. Some people will go into surgery and they will sample lymph nodes in the center part of the chest the same time as the surgery. We generally do things before hand and then we think about what the best option for the patient is and then we go forward.
- Gore I think a lot of people know people with breast cancer where even if they suspect some lymph node involvement under the arms, they do surgery and take that out, so why would you not just go in and rip out all those lymph nodes in the chest?

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- Gettinger In certain situations, we will do surgery in a patient who has lymph nodes that are in the mediastinum, the center part, if they have minimal amount of disease. If they have lots of lymph nodes that are bulky big lymph nodes there, randomized clinical trials have suggested that treating for cure with a combination of radiation and chemotherapy is as effective as surgery and perhaps less morbid and there really has been no trial that has clearly shown that surgery adds a survival benefit to curative intent, combined chemotherapy and radiation. That said, you can interpret the data in different ways and we all believe that in some situations even if you have lymph nodes in the center of the chest, surgery would be indicated.

- Gore There is a doctor at Hopkins who used to call that chemo-bemo, not sure if that is a general term over there.
- Higgins We sometimes use that.
- Gore I thought it was kind of cute. How often is the cancer amenable to surgery?
- Gettinger With screening, we are going to see more early stage cancers which are going to be treated with surgery, but at this point, the majority of patients who are diagnosed have advanced disease whether metastatic disease to different parts of the body, or metastatic to the lymph nodes, and being a medical oncologist, the majority of patients that I see already have a diagnosis of metastatic disease.
- Gore And so what do we do for those patients?
- Gettinger There are lots of things to do for those patients. The goal of therapy for someone who has a stage IV, or other words metastatic lung cancer which you can't cure, is to first improve any symptoms they are having at that point, then delay new symptoms from developing and hope to prolong survival. And the cornerstone of treatment for our patients has been chemotherapy and that has been established after many clinical trials have shown that chemotherapy improves survival and maintains or improves quality of life for patients, so it is worth it for patients. I think in the last maybe 10 years, there have been some exciting new developments in lung cancer. We have found very special types of lung cancers that are driven by certain abnormalities that we can do a lot about, for example, if a tumor has something that we call an EGFR mutation or something called ALK rearrangement, these are alternations that drive the tumor, we have pills that target those abnormalities and the vast majority of patients who get those pills will have dramatic prolonged responses to those therapies.
- Gore I think we should also probably try to cover the different types of lung cancer which we have not gotten to.

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- Higgins We are going to take a short break for a medical minute. Please stay tuned to learn more information about therapies for lung cancer with Dr. Scott Gettinger.

*Medical
Minute*

Breast cancer is the most common cancer in women. In Connecticut alone approximately 3000 women will be diagnosed with breast cancer this year and nearly 200,000 nationwide, but thanks to earlier detection, noninvasive treatments and novel therapies, there are more options for patients to fight breast cancer than ever before. Women should schedule a baseline mammogram beginning at age 40 or earlier if they have risks factors associated with breast cancer. Clinical trials are currently underway at federally designated comprehensive cancer centers, such as Yale Cancer Center and at Smilow Cancer Hospital at Yale-New Haven to make innovative new treatments available to patients. Digital breast tomosynthesis or 3D mammography is transforming breast screening by significantly reducing unnecessary procedures while picking up more cancers and eliminating some of the fear and anxiety many women experience. 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 WNPR, Connecticut's Public Media Source for news and ideas.

Higgins

Welcome back to Yale Cancer Center Answers. This is Dr. Susan Higgins along with my co-host Dr. Steven Gore. We are talking with our guest, Dr. Scott Gettinger about targeted therapies for lung cancer. Let's start with talking about the different types of lung cancer. We use this general term lung cancer, but we know that there are some very specific types and that helps us to target the therapies, maybe you can tell us a little bit about that.

Gettinger

There are two general types of lung cancer. There is non-small cell lung cancer which accounts for the majority of lung cancers, 80-85% of lung cancers are non-small cell lung cancer and then there are small cell lung cancers and the difference between these cancers can best be described by the rates of growth, the response to therapy and the prognosis, although prognosis is more driven by stage rather than type of lung cancer. Again, stage is information about where the disease is in the body, so non-small cell lung cancer, the most common type of lung cancer, can be further divided into three categories, adenocarcinoma of the lung which is the most common in the United States, squamous cell carcinoma and large cell carcinoma and small cell is small cell, so chemotherapy is again the cornerstone of therapy for metastatic disease for all these patients; however, in patients who have locally advanced disease where they have lymph nodes, again at the center part of the chest, we treat in very similar ways with the combination of chemotherapy and radiation. This is where it is very important to have a multidisciplinary team treating our patients and usually we have consults with our patients with a radiation oncologist, a surgeon, a medical oncologist, pulmonologist and sometimes other folks, for example, smoking cessation counselors and by doing this, we offer the patients the best possible therapy, I believe.

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- Higgins One of the things that patients do not see is what goes on behind the scenes at a Tumor Board and it is really important for patient care because as you know, all the physicians are there and able to coordinate their care. Maybe we could give patients a sense of what goes on there and how the decision making is made.
- Gettinger All patients we see at Yale are discussed at a Tumor Board that occurs once a week on Monday morning and we review all the scans, the pathology, any other studies that we have and we come up with a consensus recommendation as a group and there may be 25 of us, surgeons, radiation oncologists, medical oncologists, pathologists, pulmonologists and others.
- Gore Is this before they have had surgery?
- Gettinger This is before any treatment has been done for them, generally.
- Gore Gotcha.
- Gettinger Again, we come up with a plan as to what the next step is and the patient will come back and meet the folks that he needs to or she needs to meet.
- Higgins It is something that happens behind the scenes, but as a tertiary care institution, we now feel that that is the standard. If you can get all your doctors in one room with the pathologist, with the radiologist, you are going to get better communication and hopefully better outcomes. Going back to these therapies when we talking about small cell and non-small cell, could you tell us about these newer therapies like the EGFR targeted therapies and what specific types of lung cancer you target with those therapies?
- Gettinger Right now, we have approved targeted therapies really just for non-small cell lung cancer and targeted therapies are somewhat difficult to define. The idea is that you are using a targeted therapy that targets a target, so you need to have the target in the tumor and you have to know that that therapy targets that tumor. Often, targeted therapies are approved not requiring the actual target in the tumor. You just assume that there are a certain percentage of those cancers that have that target or that that target is important for promoting cancer.

Gore You mean the drugs approved for cancer, understanding that you might be using it in patients in whom it is not going to be effective?

Gettinger Any therapy, but you do not necessarily have to prove the target. For example, for lung cancer, there is a drug called bevacizumab which is in a sense a targeted therapy, it targets something called VEGF which is involved in new blood vessel formation, but we do not require a patient to have that target whether it be in the tumor microenvironment or elsewhere, so that might not be truly used as a targeted therapy although many consider it targeted therapy. I think what Susan

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was asking is what specific targeted therapies do we have for our patients where we have to show that the patient has that very unique type of lung cancer, and there are several and the three that we really need to test for in all of our patients who have non-small cell lung cancer, who do not have that squamous sub type, are EGFR, which is epidermal growth factor receptor, ALK and RAS because for all three of those special types of lung cancer, we have pills that work incredibly well. The vast majority of patients who get those pills will experience a marked reduction of the tumor bulk and clinically feel better, so those areas really have paved the way to look for other abnormalities that might drive tumors and over the last 5-10 years, we have found other types of lung cancers that are quite rare, maybe 1% of patients will have say a BRAF mutation in their lung cancer but we have drugs that target BRAF, so those drugs are being developed now in different clinical trials.

Higgins I want to digress and talk about one group of patients, and we always associate smoking and lung cancer, but there is a specific group of never smokers that have never smoked but get a lung cancer, could you speak to that for a moment about never smokers as a subset of all lung cancer patients?

Gore I was wondering about that too, we all know people like that.

Gettinger Approximately 15% of patients who have lung cancer do not have a history of smoking and that is a sizable population relative to other cancers, so more than say stomach or esophageal cancer or acute leukemia, so in and of itself that is a real entity, why patients who have never smoked get lung cancer, no one knows, it can be many different exposures, it could be some spontaneous event, there may be some patients who have a familial predisposition to having certain cancers, but what we do know is

that patients who have never smoked and have lung cancer, have a much higher chance of finding one of those abnormalities, the EGFR or the ALK, so in those patients particularly, you really need to go back and do a biopsy if enough tissue was not initially obtained to do those studies because knowing that information can profoundly affect that patient's prognosis. Well, how about smokers. Something very interesting has emerged recently, there is a new type of therapy called immunotherapy and immunotherapy is very different than chemotherapy and is very different than targeted therapy. The purpose of immunotherapy is to get the patient's own immune system to attack the cancer and we have seen some dramatic results from some of these newer therapies that allow one's immune system to do this and one thing that we have seen when we look at all the patients that have been treated and there have been 1000s of patients that have been treated with these immunotherapies, we see that patients who have a history of smoking tend to have higher response rates to these immunotherapies and the thought there is that these patients have more abnormalities in their tumor and if the tumor has more abnormalities, it is recognized easier by the immune system, so the immune system can see it and then you give these drugs that allow the immune system to do what it is supposed to do to attack these cancer.

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- Gore Dr. Gettinger does not want to toot his own horn, but in fact, you have led a lot of these studies or at least contributed very substantially to these immunotherapies in lung cancer?
- Gettinger I have and there are many patient anecdotes but I will just tell you one to give you an idea of the potential of these therapies. When we started these trials about five or six years ago, one of the first patients I ever treated was a woman who had advanced squamous cell lung cancer, had multiple lines of therapy and her prognosis was quite poor, in the order of a few months and we did not really have any other good therapies and she was willing to go onto a clinical trial and she got this drug called nivolumab. It is a drug that targets the immune system to allow the immune system to fight cancer. She quickly responded clinically and radiographically and this trial required that you stop therapy after two years. Whoever thought a patient with metastatic disease would be in that situation at two years, where they would have to stop therapy, but she and many others got to 2 years and then we had to stop therapy. Of course you can imagine she was very worried as I was because this was new, we had no experience with this drug, and that was three years ago; she has not had any therapy since then. She recently had scans again, no evidence of active disease and I do not know if I will ever see

disease and it is not just her, it is many patients, and I think this is what this new class of drugs could potentially do, could lead to long-term survival in a portion of patients on the order of years.

Gore Do you think some of these people may actually be cured? I mean can we use the cure word?

Gettinger We are reluctant to use cure, but for her, I expect scans will look good without any evidence of disease.

Gore So I imagine that patients who see you with a new diagnosis of advanced lung cancer have got to be hugely upset and anxious and worried because we all have learned over the years that in general this has been a devastating diagnosis for most people, so what is your consult like?

Gettinger You have to be realistic and put things in context and sometimes we use statistics, but there is clearly a lot of hope now with all these new therapies, these targeted therapies if your tumor is found to have these abnormalities or with immunotherapies where your tumor does not need to have anything that we need to find, so hopefully, I can instill in our patients the hope that I feel for our patients because I have seen several patients who have had a prognosis on the order of months who are out now years doing well, so I think there is reason to have hope but to have some context there and hopefully most of my consults end with hope but a grounding as to what the possibilities are.

Gore Is it important for people to stop smoking once they already have lung cancer?

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Gettinger It is always important for patients to stop smoking because it will improve their health. Will it affect the cancer that they have already, no, but they will feel better if they stop smoking and that will potentially help to prevent another unrelated lung cancer or other cancer from developing.

Gore What the radio audience did not see before was some eye contact I got from Scott because he thinks I am a skeptic about immunotherapies, but the truth is, just in the cancers that I work with which is mostly blood cancers, we have not yet seen the home runs although we hope to soon, so in fact I am just jealous that you guys are doing so well.

- Gettinger I think there is beginning to be, in some hematologic malignancies, activity with these new drugs.
- Gore Absolutely, certainly in lymphoma, in Hodgkin's disease, there is lot of activity, very interesting. It sounds like there is reason for people to be hopeful. It sounds like people really benefit from being at a center where they can get a multidisciplinary approach. Are these newer therapies that you mentioned, these targeted therapies and these immunotherapies, are they readily available or do you need to come to a place like Smilow or some other tertiary center?
- Gettinger Several of them are FDA approved, so they are available around the community and the first immunotherapy for lung cancer was approved a couple of months ago, so patients will be getting this around the community and we work with the community oncologists who have little experience with these drugs. I think when a patient is initially diagnosed, it is always a good time for a consultation and again we work with the local oncologists and at the time a patient might develop resistance to one of these therapies, then I think evaluation at a tertiary center like Yale where we have lots of clinical trials that are aimed at counteracting resistance to these drugs, I think then is when it makes it sense to come to Yale.
- Gore You mean, the patient has been responding to the drugs and now they are not?
- Gettinger The vast majority of patients who respond to therapy whether it is chemotherapy, targeted therapy or immunotherapy will develop resistance whether that is 6 months, a year, five years, or more, they will, but what we do at Yale is we do a lot of biopsies and biopsies are done with little morbidity now with new techniques and what we do is we look at the tissue now and we get the tissue before they started therapy, we compare the tissue, what changed to explain the resistance of therapy and if we can find out what changed, we could potentially offer therapy that counteracts that change and lead to response again and that is one of our goals of our research here.

Dr. Scott Gettinger is Associate Professor of Medicine and Medical Oncology at Yale School of Medicine. We invite you to share your questions and comments, you can send them to canceranswers@yale.edu or you can leave a voicemail message at 888-234-4YCC and 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 edition of Yale Cancer Center Answers here on WNPR, Connecticut's Public Media Source for news and ideas.