

WNPR: Funding for Yale Cancer Answers is provided by Smilow Cancer Hospital. Welcome to Yale Cancer Answers. The director of the Yale Cancer Center, Dr. Eric Winer. Yale Cancer Answers features conversations with oncologists and specialists who are on the forefront of the battle to fight cancer. Here's Dr. Winer. Dr. Winer: November is Lung Cancer Awareness Month. It's a time when we focus on the progress that we've made in our efforts to combat lung cancer at a time when we try to make people aware of the importance of lung cancer screening and, for that matter, lung cancer early detection. Advances in screening, and probably even more so in terms of treatment, have made a huge difference in lung cancer over the course of the last 10 to 20 years. And those changes keep occurring. Tonight, I'm very happy to have Dr. Sarah Goldberg, who is the director of the Division of Thoracic Oncology in the Yale Cancer Center. She's a professor of medicine and is a true lung cancer expert. Her research focus, which she'll tell you about later on, is largely on what are called EGFR-positive cancers — and we'll explain what that is — and on the role of immunotherapy, which is very important in lung cancer. So we have a lot to talk about, and we'll get going. Sara, welcome to Yale Cancer Answers. Thanks so much for being here. Dr. Goldberg: Thank you so much for having me. It's wonderful to be here. Dr. Winer: Yeah. So maybe we can just start with some basic numbers. How common is lung cancer? Dr. Goldberg: So lung cancer is common. It's not as common as breast cancer in women and prostate cancer in men. Those are the most common cancers among men and women. But lung cancer is second most common. So it is very common. I think where lung cancer, unfortunately, comes in first is it's the most common cause of cancer deaths both in this country and worldwide. Dr. Winer: Yeah, I mean, that's a fairly dramatic statistic. And in the U.S., how many men and women lose their lives to lung cancer each year? Dr. Goldberg: Well, it's pretty terrible. It's more than 125,000 people every year will die from lung cancer. Dr. Winer: And what about the global problem? Dr. Goldberg: So it is a huge global problem. More than 1.8 million people every year will die from lung cancer worldwide. Dr. Winer: Yeah, and unfortunately, it's estimated that that number is only going to increase. And in spite of the fact that we're doing better in the U.S., as smoking rates go up around the world and are still very common in many parts of the world, this is something we have to deal with. All right. So let's first talk about how lung cancer presents. So a new patient comes in and sees you. What are the different ways that people come to medical attention? Dr. Goldberg: It really is variable. Some people will have symptoms based on the mass or their tumor in their lung. So they might have shortness of breath or cough, sometimes chest pain. But I think just as often, people just sometimes generally don't feel well. So they might be more tired than usual. They might not be as hungry, they might be losing weight. And so sometimes it's much more nonspecific. Sometimes also, because lung cancer tends to spread to other parts of the body, unfortunately, far too often, people will sometimes present with symptoms of it in another part of their body. So they might have pain from cancer in a bone or in other parts of the body. Dr. Winer: Or even a headache and a neurologic problem occasionally. Dr. Goldberg: Exactly. We

do sometimes see that where, because the cancer spread to the brain, they'll have symptoms from that initially. Dr. Winer: And for many years, lung cancer, I think people thought, was something that if you got it, you would almost certainly die from it. That's changed. Still, for the majority of people who present with advanced lung cancer, where the cancer has spread outside of the lungs and certainly the regional lymph nodes, it's something that eventually threatens someone's life. But what about for patients with earlier-stage lung cancer? Dr. Goldberg: I tell this to my patients all the time — lung cancer can be cured. So having a diagnosis of lung cancer is not a death sentence. Dr. Winer: That's really important. Dr. Goldberg: It's really important. I think a lot of times people hear that they have lung cancer or their loved one has lung cancer and think that's the end. But it's not. Just as you said, the stage of the cancer is really important. When it's an earlier stage — so that's stage one or two or even locally advanced, which is stage three — that's when typically it's either a larger tumor or in the lymph nodes. Lung cancer can still be cured. And the ways we can cure lung cancer are with surgery and with radiation. We sometimes add chemotherapy and immune therapy to that. But those modalities, often in combination, can cure lung cancer.

WNPR: Funding for Yale Cancer Answers comes from Smilow Cancer Hospital, where patients diagnosed with pancreatic cancer are provided easy access to specialized care, including innovative treatments and clinical trials. Learn more at SmilowCancerHospital.org. The American Cancer Society estimates that nearly 150,000 people in the U.S. will be diagnosed with colorectal cancer this year alone. When detected early, colorectal cancer is easily treated and highly curable...

Dr. Winer: Welcome back to the second half of Yale Cancer Answers... Dr. Winer: Welcome back to the second half of Yale Cancer Answers, focusing this evening on lung cancer while we're in the midst of Lung Cancer Awareness Month — that is November every year. I'm joined tonight by Dr. Sara Goldberg, a professor of medicine at Yale School of Medicine and a lung cancer expert. So, Sarah, let's talk a little bit about smoking and how important it is in terms of causing lung cancer. In the past, we thought of almost all lung cancer as being smoking-related. How big a risk factor is smoking? And today, what proportion of cancers are smoking-related? Dr. Goldberg: Smoking is still the number one risk for lung cancer. It's the biggest one that we know! about. And like we talked about before, still, even though it's much less than it used to be, there still are many people who smoke now or have smoked in the last few decades, and that puts them at risk for lung cancer. Dr. Winer: Sure. let's talk a little bit about smoking and how important it is in terms of causing lung cancer. In the past, we thought of almost all lung cancer as being smoking-related. How big a risk factor is smoking? And today, what proportion of cancers are smoking-related? Dr. Goldberg: Smoking is still the number one risk factor. And those cancers tend to be a little different. They tend to have more of these driver mutations that you were talking about before — these genetic abnormalities that we can target. And the people who smoke

tend to have a different sort of cancer where there aren't these driver mutations, but there are just lots of mutations in many, many for lung cancer. It's the biggest one that we know about, and like we talked about before, still, even though it's much less than it used to be. Dr. Winer: There still are many people who smoke now or have different genes. Is that — do I have this right? Dr. Goldberg: You have it exactly right. Most or many people who have lung cancer who have never smoked will have one of these mutations that we can detect and use a targeted therapy. Or smoked in the last few decades, and that puts them at risk for lung cancer. The important thing to know, though, is that there are people who get lung cancer who have never smoked and don't even really have secondhand smoke exposure. So, unfortunately, sometimes we detect a mutation, but we don't yet have a targeted therapy available. And that's a big area of research. But yes, people who've never smoked or have a light smoking history in the it varies based on the population and where you are in the world, but probably distant past, they tend to be the people where their cancer has these driver mutations that we can sometimes target with treatments. And on the other hand, people who have smoked, their cancers have a lot more mutations. Dr. Goldberg: We used to think of that somewhere around 20% of people with lung cancer have never smoked or have a very light, distant smoking history. Dr. Winer: Sure. And those cancers tend to be a little different. They tend to have more of these driver mutations that you were talking about before — these genetic abnormalities that we can target. And the as a big problem because they weren't eligible for targeted therapies. But there's an interesting silver lining there, which is the more abnormal the cancer is, the more mutations people who smoke tend to have a different sort of cancer where there aren't these driver mutations, but there are just lots of mutations in many, many different genes. Is that— Do it has, the better a different type of treatment tends to work, which is immune therapy. Dr. Goldberg: That's right. It used to be a really big challenge when we couldn't find a target for these targeted therapies. But now we have immune therapy over the last several years, and that has really changed the way we think about treatment I have this right? Dr. Goldberg: You have it exactly right. Most or many people who have lung cancer who have never smoked will have one of these mutations that we can detect and use a targeted therapy for. Unfortunately, sometimes we detect a mutation, but we don't for those patients. Dr. Winer: So let's go down these two different paths for a minute. So for the patients who typically aren't smokers, haven't been smokers or heavy yet have a targeted therapy available, and that's a big area of research. But yes, people who've never smoked or have smokers, and they have these driver mutations, we now have multiple different drugs. And about how many drugs do we have that a light smoking history in the distant past tend to be the people where their cancer has these driver mutations that we can sometimes target with treatments. And on the other can be used in this situation? And I realize that any given patient can't receive all of them because some of them are for a mutation that someone might not have. But it used to be there were a couple of these. Now it seems like there are at least half a dozen or more. Dr. Goldberg: Oh, there's well more than that. So there's probably around nine

or hand, people who have smoked — their cancers have a lot more mutations. We used to think of that as a big problem because they weren't eligible for targeted therapies ten genes that we really have to test because we're able to target them in lung cancer. And,. But there's an interesting silver lining there, which is that the more abnormal the cancer is, the more mutations it has, the better a different type of treatment tends to work, which is immune therapy you know, we haven't really talked about the different types of lung cancer. There's actually several different subtypes. The main subtype of lung cancer where we find these mutations is the type called adenocarcinoma, and that's the most common subtype. Dr. Winer: And it's a more typically non-smoking-associated lung cancer. Dr. Winer: Yeah. Dr. Goldberg: So, it used to be a really big. It's variable. People who haven't smoked do tend to get adenocarcinoma, but even smokers sometimes will get adenocarcinoma challenge when we couldn't find a target for these targeted therapies. But now we have immune therapy over the last several years, and that has really changed the way we think about treatment for those patients. So the adenocarcinoma group is really a mix in terms of smoking history. But it's really the adenocarcinomas that tend to have these mutations. And so we really — I'm mostly talking about people who have.. Dr. Winer: So let's go down these two different paths for a minute. So for the patients who typically aren't smokers, haven't been smokers or heavy smokers, and they have these driver mutations — we now have multiple different drugs. And about how many drugs do we have that can be used in this situation? more advanced disease. That's mostly where the targeted therapies are used, although we have started to now use them in people with earlier-stage disease to try to improve our chance of cure. But we really are required to test for all of these genes in people, particularly with adenocarcinoma, but even sometimes in other subtypes, because we need to know this information. So we test, you know, And I realize that any given patient can't receive all of them because some of them are for a mutation that someone might not have. But it used to be there were a couple of these. Now it seems like there are at least half a dozen or more. Dr. Goldberg: Oh, there's well more than that. So there's probably our nine or ten genes. Actually, at Yale, in many other places, we test hundreds of genes. We actually know a whole lot about the cancer around nine or ten genes that we really have to test for because we're able to target them in lung cancer. And, you know, we haven't really talked about the different types of lung cancer. There are actually several different subtypes. The main subtype of lung cancer. But these few genes are really required. For each one, there may be several drugs available. And it does feel like every couple of months we get a new FDA approval for a new targeted therapy. So you have to really keep up with the approvals and the availability of these drugs because a mutation that we may not have been able to target a few months ago, we now might have a new treatment for where we find these mutations is the type called adenocarcinoma, and that's the most common subtype. Dr. Winer: And it's a more typically non-smoking-associated lung cancer?. Dr. Winer: So you really have to keep up. Dr. Goldberg: It's variable. People who haven't smoked do tend to get adenocarcinoma, but even smokers sometimes will get adenocarcinoma. So the

adenocarcinoma group is really a mix in terms of smoking history, but it's really the adenocarcinomas that tend to have these mutations. incredible. Dr. Winer: So, okay, nine mutations, sometimes multiple drugs for each of these. Some of those multiple drugs, you know — so let's say for EGFR mutations, some of them, am I right, are a little bit meta-ish kind of drugs, and some of them are drugs that work when the first drug no longer works? Dr. Goldberg: So EGFR is a great example to talk about, partly because it's one of the most common driver mutations that we find in lung cancer and also because we do have a lot of drugs. And it was one of the first ones discovered. So we've had now 20 years of developing drugs for EGFR. And I'm also very involved in this sort of research, so it's a good example to talk about. Dr. Goldberg: So, yes, some of the drugs, especially the older ones, worked very well, but not for very long. And so we had a couple like that, that we used to use. This is really when I was in training, when I first started practicing, and they were amazing. They shrunk the cancer, they worked really well, but it wore off quickly. And so we could sometimes sequence them, where we used one, and when it stopped working, we used another one. But what we learned over the last 15–20 years is if you have a drug that seems to be better than the other ones, it's actually typically best to use that one first. So that's really what we've done now. Dr. Winer: They keep moving up. Dr. Goldberg: Yes, they keep moving up. So it may be that we used to sequence, but when we see that this drug that we're using second or third is really so effective, in a lot of cases has less side effects, we're now moving that up to the first treatment. Dr. Winer: And is there any value in using one of those earlier, you know, first-generation drugs after you've used a third-generation drug? Do you ever see any benefit? Dr. Goldberg: Typically not. There's, you know, there's all sorts of research still going on. We do a lot of the trials here for EGFR and a lot of these other mutations where we're trying to figure these things out. How do you best sequence? A big question now, especially with EGFR, is should we be combining these drugs? Because for years we used them on their own, and they worked great. But none of these drugs, as great as they are, none of them are curing people. Sometimes they're working for years and years — I've seen people where it works ten years or more — but they're not a cure. And so we're still trying to do better. And one of the ways is to try to combine them. So we're now starting to use our best drug first and thinking about combining it with other drugs and really trying to make those treatments even more effective and work for longer. Dr. Winer: Yeah, no, it's really quite remarkable. So now let's switch to the other big group, which are the patients who don't have these targetable mutations but have cancers that have many, many genetic alterations. And there you have immunotherapy. And is immunotherapy given by itself, or is it given with chemotherapy? How do you do it? Dr. Goldberg: We have refined this over the years also by doing several different — many different — clinical trials trying to answer that question because it wasn't so obvious. And we've also, initially when it was being developed, we used it after other treatments failed and then stopped working. But now, we really have moved immune therapy to the initial treatment people get for advanced disease. We also often now will use immune

therapy for people who are eligible for surgery, who have early-stage disease. We sometimes use it before or after surgery. After radiation, we use it. So we're using immune therapy across the board in a lot of different scenarios. But to answer your question about how we use it: it depends. We sometimes do. We sometimes use it on its own as a single drug. So one immunotherapy drug — they're actually, they're called PD-1 or PD-L1 inhibitors, and there's a few different specific drugs, but that's the class. We can sometimes use it on its own, and it sometimes works incredibly well. Dr. Winer: With high expression, right? Dr. Goldberg: Exactly. We look at particular markers on the cancer cell. There's something called PD-L1 expression to help us figure that out. So with high expression, we think those tumors are the ones that are really going to do well with immune therapy. Dr. Winer: So you can use it by itself. Dr. Goldberg: Yes. And that's amazing when we can do it by itself. We can skip chemo altogether because that's really the other thing we combine it with — chemotherapy. So with the high PD-L1 expression tumors, we think just immune therapy by itself may have a good chance of working, and sometimes for a very long time. And we can give people a chemo-free regimen for their advanced lung cancer, and that's just amazing. In a lot of other cases, we are combining it with chemotherapy, and we think that helps it work better. Dr. Winer: Well, your comment about clinical trials made me remember to say that none of these advances would happen without two big things. One is truly dozens and dozens and dozens of clinical trials with thousands of patient participants who volunteer to be in these trials, hopefully to get a better treatment themselves, but also to help us make progress for patients in the future. But then the other piece is funding for research. Looking into the future, it's going to be a long time before we eliminate all deaths from lung cancer around the world, but let's just think about the United States for a minute. Could you imagine a time in 20 years when lung cancer death will be a thing of the past — not necessarily lung cancer, but losing one's life from lung cancer? Dr. Goldberg: We have done so well in the last 20 years. If that pace continues for the next 20, we're going to be doing great. I think if we improve screening and we find these cancers earlier, we have a better chance of eliminating them. And then I think with the progress, as you mentioned, with understanding the biology of lung cancer and then bringing that into clinical trials to get better drugs, I think we're well on our way. It's a huge challenge still, right? It's the number one cause of cancer deaths, so we have a long way to go. But we are making amazing, amazing progress. It's a really exciting time to study lung cancer and take care of people with lung cancer when we have so many great benefits to offer.

WNPR: Dr. Sarah Goldberg is a professor of medicine at the Yale School of Medicine. If you have questions, the address is CancerAnswers@yale.edu, and past editions of the program are available in audio and written form at YaleCancerCenter.org. We hope you'll join us next time to learn more about the fight against cancer. Funding for Yale Cancer Answers is provided by Smilow Cancer Hospital.