

Yale CANCER
CENTER

answers

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Hosts

Anees Chagpar MD

Associate Professor of
Surgical Oncology

Francine Foss MD

Professor of Medical
Oncology

**Clinical Research
Opportunities for Lung Cancer**

**Guest Expert:
Sarah Goldberg, MD**

*Assistant Professor of Medicine in
Medical Oncology, Yale School of
Medicine*

Yale Cancer Center Answers

is a weekly broadcast on

WNPR Connecticut Public Radio

Sunday Evenings at 6:00 PM

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Welcome to Yale Cancer Center Answers with doctors Francine Foss and Anees Chagpar. Dr. Foss is a Professor of Medical Oncology and Dermatology, specializing in the treatment of lymphomas. Dr. Chagpar is Associate Professor of Surgical Oncology and Director of the Breast Center at Smilow Cancer Hospital at Yale-New Haven. 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 1-888-234-4YCC. This week, doctors Foss and Chagpar welcome Dr. Sarah Goldberg for a conversation about clinical research for lung cancer. Dr. Goldberg is an Assistant Professor of Medicine in Medical Oncology at Yale School of Medicine. Here is Francine Foss.

Foss Can you start off by telling us a little bit about how long you have been at Yale Cancer Center and a little bit about yourself and your history and interest in lung cancer?

Goldberg I have been at Yale Cancer Center for just about six months now. I am originally from New York but I have been taking care of patients with lung cancer over the past three years in Boston at Mass General Hospital and Dana-Farber, and I came to Yale just about six months ago and since I have been here I have been treating patients with all sorts of different thoracic malignancies with a focus on lung cancer and clinical trials.

Foss Sarah, tell us a little bit more about clinical trials and clinical research. It seems to be something that everybody is talking about, but I think that people still might have questions about what exactly a clinical trial is, why they should get involved, and how they get involved. Tell us a little bit about all of that?

Goldberg I think you are right. We talk a lot about clinical trials in medicine and specifically in oncology, but a lot of patients have many questions about what a clinical trial even is or if it is something they should consider. A clinical trial is any sort of study where we are looking at how patients do with a certain treatment in broad strokes, so specifically for oncology and in lung cancer, we are always looking to find better treatments and better ways of taking care of our patients and clinical trials are a way to do that. Basically, when a patient is in treatment for lung cancer and we are looking for better ways of treating that patient, we may consider a clinical trial and ask them if that is something they would want to be involved in.

Foss Some people equate a clinical trial with an investigational drug or something that is experimental, can you define those terms so that patients can understand the difference between an investigational drug and a trial that involves other drugs?

Goldberg It is a very good point. All clinical trials are asking a question, in this case it's oncology and in my case, usually lung cancer, but it does not always mean that the trial involves an experimental medication or treatment. Sometimes it is two treatments that are standard and we are trying to distinguish one from the other, such as a specific patient, type of patient, or type of disease where one treatment is better than the other. So it does not always involve an experimental medication or treatment, but often we have trials available at Yale, and other places, where we are looking at

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medications that are not approved by the FDA and are not standard treatments, but we have reason to think that they might be as good as or even better than our standard treatments. So we are looking to see if that is the case by trying them in the clinic.

- Chagpar For a lot of patients, I think clinical trials are a little bit scary, because here you are, you have just been diagnosed with cancer and your doctor starts talking to you about answering research questions and something that might be experimental or investigational. Why should patients consider clinical trials, why not just do standard of care?
- Goldberg It is a good point. First of all it is something that is a very personal decision if it something you even want to be a part of. It is also something to talk to your doctor about, and that may be a doctor that you have know for a long time, or it may be the doctor that has been taking care of your cancer, or you are just meeting to take care of a new cancer diagnosis. It is something where if a standard treatment is known to be a very good treatment and has very good success rates, that may be something you want to pursue and the doctor may suggest that or it may be something where the standard treatment is not quite as good as we would like it to be, or we think an experimental treatment could possibly be better. And that is the time when the clinical trial makes a lot of sense and it is a great thing to have an in-depth discussion with their doctor about. There is also a whole research team that can be really helpful in the discussion, such as research nurses and other people who are very involved in clinical trials.
- Foss Could you talk a little bit about access to clinical trials? We are told by the National Cancer Institute that only a small percentage of patients with cancer actually enter clinical trials. What is the issue with respect to access to clinical trials and why is it that more patients aren't going into these trials?
- Goldberg At larger academic centers, such as Yale and many others around the country and the world, there are many clinical trials available for patients, but at smaller centers and in private practice offices it is less likely to have the same number of clinical trials. Part of the issue may just be that the patients are not coming to the academic centers where the clinical trials tend to be happening, but even at larger centers where there are clinical trials, many patients are hesitant to participate. Just as you brought up earlier, they are hesitant because they do not understand what it means to be part of a trial or they are worried that the treatment may not be as good as standard treatment, but again, I would encourage anyone to talk to their doctors or their nurse or people that have been involved in trials, to think about whether it makes sense for them because again sometimes you can have trials where the treatment could be better than what we have now and it is really something that I think all patients should at least consider and discuss.
- Chagpar One of the things that we often say to patients is that patients who participate in clinical trials tend to do better than patients who do not. In part because as you say, oftentimes we are comparing

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what is standard to what we think is better. We never compare what is standard to what we think might be inferior, right? Can you talk a little bit about that concept because I do not think that is something that a lot of patients understand? Also maybe talk a little bit about all of the regulatory framework that houses clinical trials that might make it a little bit less scary for patients who are thinking about whether or not they want to participate in the clinical trial?

Goldberg First of all, there are a lot of regulations behind clinical trials and so every trial that is in any center that you may be going to, to see a physician, has been reviewed very carefully by a panel of people who are experts in trials and research to make sure that it is something that is likely to be safe for the patients and something that is not likely to be worse than our standard treatment. Just as you were saying, either there is something we think may be better or something we think may be the same, but maybe with less side effects. All this has been very well discussed and studied to try to make sure it is something safe and at least more effective for our patients if not the same. I think a misperception about trials is that you might be put in a group that has a placebo, or what people call a sugar pill, so you might be getting nothing, and that is really very uncommon in oncology trials specifically, but in many other trials as well. Very often we are comparing a newer treatment with an existing treatment. It is very rare to get nothing on a clinical trial, to get no treatment or no active treatment. I think that is something that is not likely to happen in cancer clinical trials, it is a treatment that is standard, usually compared to a treatment that may be better, or even on many trials all patients get just one treatment.

Chagpar And if you ever were on a placebo controlled trial, or a trial in which the comparator was a sugar pill, you would be informed of what the two arms were, correct? You would always know what was on the trial, a lot of people have this perception that they do not know what the two arms are and that there are some sort of secrecy behind it.

Goldberg That's right, and every trial that anyone would go on would have a large packet of information that would give you every detail you would need to know about the trial, you would know all possible side effects, you would know the possible groups you may be in whether everyone gets the same treatment or some people get different treatments, but it would all be there in print that you can take home and look over carefully so that you are very well informed before you would ever decide to participate.

Foss One of the things that many cancers centers are doing, and the NCI is doing, is trying to get these trials out of the big academic centers into the community setting. Can you talk a little bit about the importance of that? I am sure for lung cancer, which is a common cancer, that it is going to be critical to make these trials accessible to patients.

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- Goldberg I think that's right. Especially in lung cancer where it's such a common disease and patients do not always want to travel into cities to come to the bigger academic centers, they want to stay with their physicians that may have been treating them for years, and especially now that we have so many clinical trials with really exciting medications or treatments where we have more potential than we ever had before in lung cancer, and in other diseases too, it is so important to get these trials into other centers and other sites into the community, into physician's office and we are actively trying to do that now in thoracic oncology and lung cancer and in other cancers. I know at Yale we have several sites in the community that we're associated with and we are working to open trials there so that you don't need to come to a bigger hospital to get on one of these trial that may be available right in your own town and I think that is a such great resource for patients.
- Chagpar One of the things that we talked about in terms of advantages of clinical trials is that you can potentially avail yourself of newer treatments, more effective treatments, treatments with less side effects, but the other advantage I think of participating in a clinical trial is really more of an altruistic one, in the sense that you are helping to move the frontier of cancer management forward and to help advance the field. Do you want to talk a little bit about that and whether you see that as a motivation for patients to participate in clinical trials or whether you think that is something that is not really on their radar?
- Goldberg I hear patients tell me all the time that they want to participate because they have to deal with this disease and they have to undergo the treatment and if there is anything that they can do to help others in the future, they want to do that. And so I see clinical trials as a way for patients to get treatments that may be better than what we have now and I think that many patients see that too, but they also see it as a way of helping others. Yes they need to go through this and they have to be part of the trial, but maybe one day this will become the standard and it will be better than what we have now. So I completely agree, I think that many patients do this in an altruistic way and that they want to help others who may be going through something similar.
- Foss One of the things that we are hearing a lot more about now is personalized medicine, in a way taking the tumor, looking at it, and deciding what treatment the patient should have. Can you talk about the interface between personalized medicine and clinical trials?
- Goldberg Personalized medicine is something that we are all very excited about in lung cancer, and in other cancers as well, but I think lung cancer has really made a lot of headway in that area. Personalized medicine in general means finding some characteristics about the cancer or the tumor and matching a drug with it that is likely to work better because of that characteristic in the cancer, so personalizing the treatment to the disease itself instead of treating all lung cancer the same, we try to match the disease with the treatment. It is something that has been developed over the last several years. Clinical trials now, in lung cancer in particular, are very much focused on personalized medicine in that we do not necessarily want the types of treatment that have traditionally been in oncology, which are one size fits all. We are looking for treatments where we

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think that one specific medication or treatment is the right one for that patient or that tumor so that is the type of trial we are very focused on, it is not all of our trials but many of them are personalized medicine trials and what that means logistically for the treatment on the trial is that we would take a small piece of the tumor that is removed from the patient and study it to find out its characteristics and then try to match those characteristics to a study treatment or treatment on a trial and we hope that will give the patient the best chance of doing very well with that.

Chagpar That is excellent. We are going to take a short break for a medical minute. Please stay tuned to learn more information about clinical research opportunities and personalized medicine in lung cancer with Dr. Sarah Goldberg.

*Medical
Minute*

There are over 12 million cancer survivors in the United States right now and the numbers keep growing. Completing treatment for cancer is a very exciting milestone but cancer and its treatment can be a life changing experience. The return to normal activities and relationships may be difficult and cancer survivors face other longterm side effects of cancer including heart problems, osteoporosis, fertility issues, and an increased risk of second cancers. Resources for cancer survivors are available at federally designated comprehensive cancer centers such as the one at Yale Cancer Center to keep cancer survivors well and focused on healthy living. This has been a medical minute brought to you as a public service by Yale Cancer Center. More information is available at yalecancercenter.org. You are listening to the WNPR Health Forum on the Connecticut Public Broadcasting Network.

Chagpar Welcome back to Yale Cancer Center Answers. This is Dr. Anees Chagpar and I am joined today by my co-host Dr. Francine Foss. Our guest today is Dr. Sarah Goldberg and right before the break we were talking a little bit about personalized medicine in lung cancer and clinical research. Tell us a little more about your specific research and the clinical trials that you are doing and personalized medicine, I hear that you are doing some outstanding work.

Goldberg Some of the work that I am doing at Yale involves just what we were talking about earlier which is personalized medicine in cancer research and specifically my area of interest and focus is in EGFR mutations in lung cancer. We have been learning a lot about lung cancer over the last few years and researchers have figured out that there is not just one type of lung cancer, there are actually many types that can be divided based on the specific mutation or alteration found in the cancer cells and one of the more common ones is a mutation called EGFR. It is a mutation in the EGFR gene, and over the last several years clinical trial have shown us that there are several medications that work very well for patients who have this specific change in the EGFR gene, an EGFR mutation in lung cancer. So my research focus is on that and tries to make those treatments even more effective than they already are by combining different treatments and trying to use them earlier on in treatment instead of later on and trying to help the patients live for as long as possible.

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- Foss Is this EGF receptor something that is tested routinely in lung cancer specimens, would a patient for instance know whether their EGF receptor is mutated?
- Goldberg It is becoming more and more common that it is being tested in lung cancer for most patients with advanced disease. There are several different types of lung cancer and it is non-small cell lung cancers where we are mostly testing for EGFR, and I think that's because now we have such effective treatments for these patients who have EGFR mutations, it is very commonly tested. We do not always test when patients have an earlier stage lung cancer that can possibly be taken out by surgery, because it is not information we can use, those patients undergo surgery and some others may get radiation therapy, but they would not necessarily get medication that would be important to know their EGFR mutation status.
- Chagpar You talk about this being a mutation in the EGFR gene and I think a lot of times these days we talk about genes and gene mutations and genomics. Tell us a little bit more about that, is that what this is and where do you see this field going?
- Goldberg EGFR is a gene that is in all of your cells, in some lung cancer cells that gene is altered, it is changed, and it is what drives the cancer to grow. The reason it is so important in research and in treatment is that we have a drug that inhibits that abnormality and can cause the cancer to stop growing. The field in general is looking for different alterations such as EGFR because if we could find them in cancer cells and we can find a drug that matches that, then we can treat those patients much more effectively and we have been very successful in some diseases. In lung cancer of course there is EGFR as we have been talking about, and there are other mutations that we have found such as ALK and others. And in other cancers, not lung cancer but other cancers, we found other mutations where specific targeted treatment can be very be effective. I think this is entirely the future of cancer treatment, possibly not for all cancers, but a good portion of them where we are finding alterations and finding the right treatment that matches that and I think that is more effective for many cancers than anything else.
- Foss Can you tell us how effective these new treatments are? Are we curing patients with these treatments? What really is the goal and the outcome for most patients getting these new drugs?
- Goldberg So these new drugs are used, as I said before, in patients with more advance disease where we cannot necessarily remove the cancer with a surgery or with radiation, and the patients can have really incredible responses to these treatments where the cancer shrinks and patients feel so much better in even a matter of days if these mutations are found and we have the right drug to treat it and patients can do very well for very long period of time. It would be unlikely that any of these types of treatments could cure that disease, which is the unfortunate nature of them, that eventually even though the treatment was so effective, they tend to stop working over time. Now the research goals are to try to figure out newer and better ways of inhibiting those specific alterations in cancer

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with drugs that are possibly even better than the ones we have now, or possibly combinations, using them in different ways to try to cure the disease because we are not quite there yet and I think that is why I am personally so excited about research and clinical trials and I think a lot of people are because we have so much success now and we are so much better than we have ever been before but we are not quite there yet and we still have a long way to go before we get there.

Chagpar One of the questions that I think a lot of people have is the difference between genetics and genomics. People are likely listening at home thinking, when you talk about these mistakes or these alterations in genes in a tumor, people often have heard about genetics in terms of well my parents have this and my grandparents had this, so are those two things the same or are they different, can you tell us a little bit about that?

Goldberg I hear this a lot from my patients, because it is something a lot of people think about and you hear something happened in a gene and you worry you could pass it along to your kids, or, did I inherit this? These types of mutations are completely different than when you talk about those types of genes, so it is true that you inherit your genes from your parents and you can pass along genes to your children, but these types of mutations in these specific genes are only found in cancer, the ones that I am talking about for lung cancer, and so it would be very unlikely that it would be something that you have inherited or that you could pass along. These are in almost all patients with lung cancer who have these and they are just mutations and changes in the genes and in the cancer themselves and because of that you did not inherit it and you can't pass it along, it is something that happens within the cancer.

Foss Some patients talk about, what caused this, and I think with lung cancer obviously smoking is a factor, but for patients with these mutations, are there other factors that they need to worry about? Are most cases of lung cancer now associated with smoking?

Goldberg Smoking is a very big risk factor for developing lung cancer, but it is definitely not the only one and we know that because there are many patients who have lung cancer who have never smoked, or may have smoked a little many years ago. So it is not the only thing, and then of course there are many patients who do smoke, who do not get lung cancer. So there is obviously more at play here than we really understand. I think for people who smoke, it is always advised to quit smoking if possible, because the risk of lung cancer does go up with smoking, but there is more that again we just do not know yet, and in terms of other risk factors, there is really not much else that we are able to point to for most people.

Chagpar We started to talk about why do some people get cancer and other people do not? Some people have talked about the immune system and how that plays into cancer development and cancer

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progression. Can you talk a little bit about that and about whether in fact researchers are starting to look at the immune system and how it interplays with cancers and cancer therapy?

Goldberg We are definitely very excited about how the immune system is working to fight cancer. We have known for a long time that the immune system can fight off some cancers, but for many cancers and lung cancer is included in that, it does not do it on its own. Our own immune system should be able to fight cancers, but there is something in the cancer that defends itself against it so our own immune system is not able to ward off many lung cancers that develop, but now a big focus in researching lung cancer is trying to get your own immune system to do what it should do, which is fight off the cancer, and there are several therapies now that seem to be very, very promising in this regard and it is another big area of research. It is something that at Yale we are all really excited about in lung cancer and another cancers as well including melanoma and kidney cancer. There has been very exciting early clinical trial data showing that medications that help the immune system fight cancer can be really effective.

Foss Sarah, we have heard about the PD-1 therapies and how exciting they are in other kinds of cancers. Can you talk about that specifically and tell the audience what it is and how it relates to the lung cancer treatments that you are talking about?

Goldberg PD-1 is the therapy you are talking about and the drugs in general are called anti-PD-1 or anti-PD-L1, those are the two classes of drugs, and there are several different treatments and drugs that are in those two groups, those are the general types of treatments and basically those drugs are trying to do just what I was saying a minute ago, help your own immune system fight off the cancer, helping your own immune cells that you already have recognize the foreign tumor, which should not necessarily be there and helping it fight it off and it does not seem to be effective for all sorts of cancers and it does not seem to be effective even in all lung cancers, but in some patients, a good number of patients, we have seen tremendous responses and a lot of shrinkage of disease and patients can do well on them for a long period of time and it is something that it is so exciting for us now and it is something where we are working to open other trials of these drugs because they are still in development. They are not standard medications yet, but I am really hopeful that one day they will be.

Foss That is really exciting, Anees and I both trained a lot longer ago than you did and at least when we trained I do not think anybody thought for one minute that an immunotherapy would be effective in lung cancer. This is really paradigm shifting research.

Goldberg It is, there are other cancers where we have thought more optimistically about immune therapy. Melanoma is a disease that we have been using immune therapies in for some time trying to find different ways to help the immune system fight off cancer, and that seems to be effective in some patients, but I agree, in lung cancer it was never one of the diseases even on the radar for having the immune system fight it off. It seemed to just be too impossible and there have been several

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different areas of research over many years, vaccine trials and others, where there is still research going on, but none yet that has been as exciting as this anti-PD-1 and anti-PD-L1 therapy.

Chagpar This brings us back to the importance of clinical trials and the fact that the patients who participate in trials like the trials that went on with anti-PD-L1 and other immunotherapies really benefit from these dramatic responses that we have never seen before. So for therapies like that that are immunotherapies that are rather novel, one would presume that these are therapies that may only be found in larger academic centers, or can you go to your local oncologist in a smaller town and get this therapy? Or is this something where people really need to get to a larger academic center?

Goldberg The trials that have already been done were the earlier trials that for the most part I think were at larger academic centers and that tends to be the case, that the earlier trials where we are paying very close attention to the side effects, because we are not familiar with them yet, those tend to be at larger academic centers. Now that several of these medications have been tried in earlier trials and now are moving on into later trials, I expect that they will be open in other centers that may not be larger academic centers, but I know that the larger centers will also have these trials. Because we are all excited about it, we are trying to open as many of these trials as we can and really trying to get our patients access to these medications that may be exciting and effective.

Foss Sarah, just in the last minute, can you tell us what you think is the most exciting thing coming up in the future? You mentioned PD-1, but are there other things that we should know about in lung cancer?

Goldberg For every individual patient there may be something specific that is the most exciting for them. So based on what their tumor shows us, I think we will be able to match the right treatment. If a patient has an EGFR, there may be a specific personalized targeted therapy that is the most exciting for them. In another situation it might be the immune therapies that are the most exciting, so I think in general the most exciting part about lung cancer research and oncology is finding the right treatment for the right patient.

Dr. Sarah Goldberg is Assistant Professor of Medicine in Medical Oncology at Yale School of Medicine. If you have questions or would like to add your comments, visit yalecancercenter.org where you can also get the podcast and find written transcripts of past programs. You are listening to the WNPR Health Forum on the Connecticut Public Broadcasting Network.