What every EGFR patient needs to know

Diane Mulligan:

It wasn't very long ago that a lung cancer diagnosis left patients with very few options for treatment. Chemotherapy, radiation, maybe surgery were the only treatments. And the five year survival rates were just terrible. But today, just a few years later, so much has changed. I'm Diane Mulligan.

Sarah Beatty:

And I'm Sarah Beatty. Biomarker testing is nothing short of a revolution in lung cancer treatments. And today, we're talking to someone who had a part in discovering the first lung cancer biomarker, which gives people living with EGFR lung cancer, much better treatment options.

Dr. David Carbone:

And so I think it's a very satisfying aspect of being both a researcher and a clinician to try to figure out the best treatment for not a thousand patients, not everybody, but that one person who's sitting in front of you, it's my job to figure out the best treatment for them.

Diane Mulligan:

Lung cancer is a tough topic. It's a disease that affects patients, families, friends, coworkers. But first, it's a disease that affects people. The Hope With Answers: Living With Lung Cancer podcast brings you stories about people living, truly living with lung cancer. The researchers dedicated to finding new breakthrough treatments and others who are working to bring hope into the lung cancer experience. Dr. David Carbone is a lung cancer clinician, researcher, and specialist at the Ohio State University Comprehensive Cancer Center. He's been working on developing treatments for lung cancer for years. And played an important role in discovering the first targeted therapy aimed at the EGFR biomarker.

Sarah Beatty:

Today on the Hope With Answers: Living With Lung Cancer podcast, we have the amazing opportunity to learn more about the EGFR biomarker from Dr. Carbone. Information that everyone whose life is affected by EGFR should know. Dr. Carbone, we are about the EGFR biomarker today and at a really, really basic level to get started, can you explain what a biomarker is?

Dr. David Carbone:

So you can understand that there might be a variety of definitions of a biomarker. But fundamentally, I think a biomarker is some feature of a tumor or a patient that you can measure that helps guide what you do or how you treat that patient. And EGFR is a great example of a biomarker that's a tremendous utility.

Sarah Beatty:

So we're going to get into some of that today. Again, at a fairly approachable level, does EGFR lung cancer affect some populations differently than others?

Dr. David Carbone:

Well, it's certainly more frequent in some populations than others. So, in Asia and some Asian countries, the frequency of this biomarker is in the 50 or 60% range. Whereas in Spain, it's two or three or 5%. So it definitely varies from one population to another. But the bottom line is that if you have an EGFR mutation and you're African American, the implications for your treatment are really the same. If you're Japanese, it just, the frequency of finding that alteration is different.

Sarah Beatty:

That's really interesting. So one of the things that LCFA works on, one of the LCFA's goals is making sure that everyone has access to comprehensive biomarker testing. Can you give us an idea of what comprehensive biomarker testing gives you as a doctor and the patient when it comes to someone with EGFR who's gotten that information back that they have EGFR lung cancer?

Dr. David Carbone:

Yeah. So again, the definition of comprehensive can vary from one situation to another. But, right now there's maybe 10 or 12 different things that you can measure about a tumor that dramatically affect the type of treatment you choose for that patient. And historically people have said, "Well these two are more frequent than the others, so we'll only measure these two. And if they're negative, then we'll measure another one." But really, it's very clear to me that, for optimal patient care and getting the right treatment to the right patient as rapidly as possible, it's very important to measure for an entire panel of these markers all at the same time and before any treatment decision is made. Because as I said, it radically changes the best treatment options for that patient if you find one of these markers.

Sarah Beatty:

That's a really good thing for people to understand. So I also understand that EGFR is one of those biomarkers where a liquid biopsy, which sounds really complicated, but it's really just a blood test like, we're all used to getting [crosstalk 00:06:00] in physical. The standard blood test is generally accurate and useful in terms of treatment. What can a liquid biopsy or one of these blood tests tell you about a patient's lung cancer?

Dr. David Carbone:

Well, the EGFR is an example of a biomarker that's tested in the DNA of the tumor. And historically you've needed a sample of the tumor in order to test for that biomarker in the tumor DNA. But now this blood biopsy technology has really developed to a pretty advanced state, and so that these biomarkers which are mutations or alterations in the DNA and the tumor, can actually be measured at tiny amounts of them get into the peripheral blood, and you can measure it in the blood. And if you find this specific alteration in EGFR in the blood, then it is

safe to act on that information and choose the EGFR appropriate treatment for that patient. And that's extremely important because very often we get patients who have tiny biopsies that aren't big enough for genetic analysis, or they have some urgency that they need to get treated right away. And you don't want to schedule a tissue biopsy that's adequate for tissue testing.

Dr. David Carbone:

If you get a positive in a blood biopsy, just from a blood sample, then that's sufficient to act upon, like I said. The problem with blood biopsies is, it's not quite as sensitive as a tissue analysis. So, there are a significant number of patients whose tumors truly have this EGFR biomarker that the blood analysis does not pick up. And so in general, I don't rely only on a negative blood biopsy. The blood biopsy doesn't show anything, then I will look with a tissue biopsy. Because it, as I said, it makes such a huge difference to the way you manage patients. It really is tragic if you miss even one patient, if you miss this finding in even one patient and choose the wrong treatment for them, you're really doing them a disservice. So we try to look very hard for these markers.

Sarah Beatty:

When you start to look at the EGFR biomarker, things get really complicated very, very quickly. We talk about EGFR and ALK and ROS1 and a couple others [crosstalk 00:08:57].

Dr. David Carbone:

All these acronyms, you get the similar like the military or the [crosstalk 00:09:00].

Sarah Beatty:

Right. And you think, oh, golly, like, it's just that complicated. Well, then you start to look at EGFR, and now there's Exon 18, 19, 20, 21.

Dr. David Carbone:

Exon 19, Exon 20 Right. Point [crosstalk 00:09:12] deletions right.

Sarah Beatty:

Good golly. I mean, this just gets so complicated. So can you help us understand what these, those are called subtypes or comutations? Like what information is that Exon string of numbers giving us?

Dr. David Carbone:

Right. Well, that's a question with a long answer and a short answer. But basically, as I said, the biomarker EGFR is a mutation in the DNA that turns on the gene called epidermal growth factor receptor. And it turns out that there's many different ways the DNA can be altered in order to turn that gene on. The two most common ones are called, Exon 19 and deletion and L85R. L858R, which is an Exon 21 mutation. And I have a PhD in genetics, and I don't expect patients to have a PhD in genetics or most doctors to have one. But the letters, the description that I just

used describes exactly the alteration in the DNA that's associated with this activation. So the most common is Exon 19 deletion, and the gene is divided up into pieces called Exons.

Dr. David Carbone:

And so, there's a piece of the gene that's Exon 19. And that alteration is a deletion of usually five amino acids in that protein, and that's the deletion 19. Whereas the second most common mutation is L858R, which is a point mutation of leucine, which is an L at position 858, to an arginine, which is designated as an R. Now patients don't really, don't really need to understand all the details of this, but it's extremely important for their physicians to. Because, you can't just say there's a mutation in EGFR, and that determines the treatment. Some of these mutations, the less common ones typically, have a totally different drug sensitivity pattern, and you should use completely different drugs and the more common one. So it is important to know, not just that your tumor has an EGFR mutation, but precisely which alteration the tumor's DNA has. And that makes a difference as well.

Sarah Beatty:

So I want to stop just for a tiny moment here and talk about because, I mean, that was so much information. And I talked to a doctor a couple of weeks ago who, and she's a hospitalist, a generalist. Who works on the oncology ward now, and she says, "The number of people that I see with lung cancer, who've never had biomarker testing is really, really frustrating." And so I just want to, at this point, make sure for anybody who's listening for the first time, everything that you have talked about is what you can and should expect a thoracic oncologist to be able to ask those questions and then translate those answers. Is that right?

Dr. David Carbone:

Well, certainly a thoracic oncologist. So at my institution we have 10 medical oncologists who do nothing but treat lung cancer patients. And they're expert at all of these aspects. And I have full confidence that they do the right thing when it comes to biomarker testing. But in the community, when you have a solo practitioner who treats every kind of cancer, breast cancer, colon cancer, sometimes even leukemias and lymphomas, and they have to keep up to date in all those different cancer types, it's extremely hard and very daunting to know all the details that are now important for treating a lung cancer patient. So, part of the mission of foundations like yours is really to empower patients to at least understand that their tumor needs to be tested for these things and ask their doctor about them. These are very well spelled out in the oncology guidelines, the NCCN guidelines for the basic biomarker testing that should be done.

Dr. David Carbone:

And potentially, if they're not confident that the right thing is being done to get a second opinion. And it is really important to get the right treatment first. So a doctor in the community may say, "Fine, you can get a second opinion, but I'm going to give you a dose of chemotherapy just because lung cancer is a bad disease." That's generally a bad decision because, if you get a dose of chemotherapy and immunotherapy, which is more typical, that can increase your risk of complications from, if you end up having an EGFR mutation, for example, it also costs a lot of money and it can delay starting the right treatment. And it also eliminates the possibility of you

participating in a first line clinical trial. So don't start a random treatment just because it's available, start the right treatment after the right testing.

Sarah Beatty:

Well, let's talk about the right treatment for just a second. You have mentioned two and we'll get to both of them. But, the first one is a targeted therapy. What targeted therapies, and you can kind of explain what a targeted therapy is. What targeted therapies are available to someone with EGFR and its various subtypes?

Dr. David Carbone:

Well, there are many. The two most common mutations are sensitive to most of them. But the most current generation targeted therapy for the common EGFR mutations is osimertinib. And it's been developed as a selective inhibitor of just the mutant form of this protein and not the normal form, since every cell in your body has the gene and many other cells, particularly skin and gut have actually expressed the protein as well. So, it's been found that, that drug has a very good efficacy and a low toxicity, and is the most commonly prescribed first line treatment. It also has the advantage of having good brain penetration, and these types of tumors often spread to the brain and the osimertinib can prevent the development of brain metastases or even treat the ones that are found at diagnosis. Some of the other mutations, as I said, though, are better targeted with other drugs.

Sarah Beatty:

So is it right to say that these targeted therapies are designed to work with a really specific-

Dr. David Carbone:

I didn't define targeted therapies for you, did I? So, the way we refer to targeted therapies is a therapy that targets one of these specific alterations that we've been talking about. So the EGFR gene is a gene that controls the growth of many cells in your body, and that's how it was discovered. And the cancers have found that if they can switch this gene on in an abnormal way, unregulated way, that, that causes the cancer to grow in an abnormal unregulated way. And in most tumors with this alteration, really the EGFR gene alteration is the primary driver of that cancer's growth. And that's why we call these alterations driver alterations or driver mutations.

Dr. David Carbone:

Well, that's fortunate if you only have one Achilles' heel or one feature of a cancer, that's driving it, then if you're smart and science is found, but there are specific drugs that can turn that specific gene off. They can make the drug target that gene specifically and turn off the alteration that was turned on by the mutation. And so what we find is that, we can give these drugs, which are usually oral drugs, that they turn off this alteration specifically in the cancer cells. And sometimes almost like magic, the cancer melts away and the patients often have no side effects at all. It's really a dramatic efficacy that we see when you have a known driver and you have a drug that targets that driver.

Sarah Beatty:

That's amazing. So one of the other things, and you just mentioned it a moment ago, that we hear about a lot is, immunotherapy. And sometimes they're in combination, but let's talk sort of isolated here about immunotherapy. And that's the idea of kind of harnessing the body's own immune system to fight lung cancer. So is immunotherapy effective for someone with the EGFR mutation?

Dr. David Carbone:

In general, not. Now, does that mean that we never use it? No. There are situations where we use immunotherapy with virtually every type of lung cancer, but it is the wrong treatment as a first treatment for EGFR mutated lung cancer. The response rate is extremely low for immunotherapy and very high for targeted therapy. And with the modern targeted therapy drugs, it's definitely the wrong thing to start with. Now, there are regimens that include immunotherapy and after the tumor becomes resistant to targeted therapies. But it's definitely the wrong thing to do to start with immunotherapy if you have a EGFR mutated tumor.

Sarah Beatty:

That's good for people to know. So you mentioned a little bit ago that, targeted therapy generally is a pill. So, that's fairly easy to take, you can take it home, you don't have to go to like an infusion center. It's not a clinical setting to take this medication. And in general, is it right to say that a targeted therapy doesn't have the kind of side effects that something like a chemo or radiation might? Or, is it not right to say, oh gosh, it doesn't have any side effects.

Dr. David Carbone:

Well, these are all powerful medicines designed to treat a life threatening disease. And so I think it's safe to say all of the treatments for lung cancer have some potential for side effects, include even the best targeted therapies. And many people take chemotherapy with very tolerable, minimal side effects as well. But, I think it's safe to say that most people who take targeted therapy for EGFR mutated lung cancer have very few side effects that are very tolerable. And primarily a mild skin rash, though, many people have none. Or slightly looser bowels than normal, that is readily controlled.

Dr. David Carbone:

And the thing with side effects is it's dependent on the type of treatment. So the side effects for immunotherapy are really totally different than the side effects for chemo, totally different from the side effects of targeted therapies and even different targeted therapies have different side effects. So, every time a patient starts on these, the doctor and the nurse should really explain to them what they might expect and how to deal with it.

Sarah Beatty:

You mentioned a little bit ago, clinical trials, participating in a clinical trial. And I wonder if you can talk through why someone living with EGFR lung cancer might participate in a clinical trial. And maybe you could even expand on it to say, when might they participate in a clinical trial?

Dr. David Carbone:

Well, even though cancer treatment has advanced dramatically in the 35 years, since I've been treating lung cancer patients, the treatments we have are good, but they're far from perfect. With the modern drugs for EGFR targeted therapies, we get response rates that are super high. And 80, 90% of patients have substantial benefit from these drugs, but not everyone. And these drugs are generally not curative so that when you treat a patient with EGFR mutant lung cancer with osimertinib, they can have a dramatic response that can last years. But in general, I tell patients, if you live long enough, the cancer will become resistant to this drug and we'll have to look for a plan B. And so, even though we've come a long way, I think that there's some very exciting research that's going on now, for example, to make the depth and duration of the efficacy of these targeted agents, better from the very beginning of treatment.

Dr. David Carbone:

And so we have a trial that we now have are treating patients on. Combining osimertinib with a drug that targets beta-catenin, which is a resistance pathway. And so, I think that's a worthwhile trial to be enrolled in. But also when the tumor becomes resistant, there are trials trying different drug combinations and alternative drugs to treat patients whose tumors have become resistant to first line therapy. So, I tell patients that clinical trials are tomorrow's drugs available today. Tomorrow's standard of care available now is part of a clinical trial. And with these imperfect treatments, I think it's very reasonable to consider clinical trials at every stage in your cancer journey.

Sarah Beatty:

It's so wonderful these days is that, you talk about a plan B, but people are living long enough at this point, thanks to these wonderful-

Dr. David Carbone:

C and D and E and F.

Sarah Beatty:

Yeah. Which is just, I mean, that's just amazing. And it's such a serious topic and there's so much serious work that does need to happen, but I think every now and again, it's kind of nice to think, my gosh, C and D and E and F and whatever, because there are people living with it. And thanks to this kind of research.

Dr. David Carbone:

Well, even beyond drugs or trials, we now often treat patients what we call beyond progression. So, a patient will be on the drug, they'll have 20 sites of disease, all of them will shrink nicely, but then one will grow. And now we can used targeted radiation, for example, or even surgery to treat that one escaping tumor, and then continue the drug. And sometimes for years beyond that are able to control the general disease. So we've learned in not only to switch to different therapies, but how to better manage a patient on their first line therapy.

Sarah Beatty:

That's amazing. So, we've kind of talked about that a little bit here. One thing, and you just mentioned this, that is very common in lung cancer is that, with the right treatment it can be controlled for a while, but it has a really nasty tendency to, what's called, develop resistance to various treatments. And meaning that treatment quits working and the cancer starts growing again. What does this mean? What does that information mean for someone who is living with EGFR? Does that happen more or less often with somebody with EGFR lung cancer?

Dr. David Carbone:

All of the targeted therapies eventually lose efficacy and the tumor becomes resistant. And for a given patient, it could be three months, it could be three years, it could be 10 years before the tumor becomes resistant. So it's difficult to say in a given patient. There are what we call comutations that can alter that course. So, if a patient's tumor has the EGFR mutation and another gene called P53, they tend to have a shorter duration of efficacy than if they don't have the P53. But, nobody can predict what will happen for a particular patient. And that's why we often do another genetic analysis when the tumor starts to grow again in a multifocal way. Because sometimes we can identify, what we call bypass pathways that can be targeted such as met or transformation to a different of cell, which is treated differently like small cell lung cancer. So often we'll do a biopsy at the time of resistance development to see if we can find a smart plan B.

Sarah Beatty:

Got you. Well, and it's so interesting because that's kind of my next question is that, and this is my rough understanding, so I hope you can illuminate me here. EGFR has kind of a tendency to turn into, so EGFR non-small cell lung cancer has a tendency to turn into small cell lung cancer. And I wonder if you can give us a little bit of information about that. Do we know why that happens? And what does that do? You just mentioned that you do another biopsy at that point, and then what information do you find and how does that affect the course of treatment?

Dr. David Carbone:

So we know a little bit about that process. Small cell lung cancer characterized by mutation of two different genes called P53 and RB. And it also looks different under a microscope. And it's been found that especially if you have non-small cell lung cancer, with the EGFR mutation. But if it also has a P53 and an RB mutation, then that tumor tends to escape control from the targeted therapy by transforming into what looks under a microscope like small cell lung cancer. Now this small cell lung cancer still has all the same mutations. And so to me, it's technically not correct that the tumor becomes resistant because it's small cell, it becomes resistant because it's resistant to the drugs, but it looks like small cell under a microscope.

Dr. David Carbone:

And so therefore we treat it like small cell in practice with a chemotherapy, a regimen, and sometimes radiation as well, and sometimes we continue the EGFR targeting as well. It certainly, we're not as good at treating these transformations or these resistance mechanisms as we are in treating the initial disease, which is why I personally am focusing on that very first treatment, how to make it more effective and last longer. So we're not chasing resistant tumors, we're trying to kill it day one and have it not come back. That's my goal.

Sarah Beatty:

Get it in the first place. You and I have talked a number of times and you have this incredible depth of experience and background. You've been battling this for a handful of years.

Dr. David Carbone:

Yeah. More than a handful.

Sarah Beatty:

But I understand that you're one of the researchers who discovered EGFR and its importance in treating lung cancer. Can you just from your vantage point as, from the beginning of your career where all of this was absolutely cutting edge and there was really only a plan A, to now being able to talk about all the information that you're able to act on through biomarker testing, different treatments, different options, testing again. How did the discovery of EGFR come about? And what's the place of it in the sort of history of treating lung cancer?

Dr. David Carbone:

Well, again, that's a question with a long answer and a short answer. But basically the EGFR pathway was discovered just by a very smart, basic scientist doing basic research on how cells grew and how they stopped growing. And there's a guy named Stanley Cohen who found a substance that caused rat's eyes to open faster and their teeth to grow faster, and he called it epidermal growth factor. And it was found that when you throw this stuff on cells, they grow faster. And so, people developed drugs that blocked that receptor, but they had no idea that they were activating mutations in EGFR. And so, these drugs were applied in clinical trials in unselected patients, and almost none of the patients had any benefit. The tumor just kept growing, and it didn't really care about that drug.

Dr. David Carbone:

And then a few patients had dramatic durable responses. The next scan you do, shows like, almost complete resolution of the cancer. And that tells you that there's something different about that person's tumor compared to the person whose tumor didn't respond. And so it was actually back in 2002 that I had a patient that had a dramatic response just in one of these trials where most people didn't respond. But he had a dramatic and durable response, and we decided to look to see if the EGFR gene was structurally different in his tumor and it turns out it was. And we presented that at the AACR meeting before the papers describing it came out.

Dr. David Carbone:

But it turns out that, that these alterations in the DNA of this subset of tumors, really is a great biomarker for picking patients to use for this targeted therapy. And that kind of matching of drugs to tumor characteristics or tumor biomarkers really revolutionize the field of lung cancer therapy into one where we tailor the treatment to the tumor characteristics like we've been discussing. And really has made dramatic differences in patients lives taking patients that are near death and bringing them back to a normal quality of life, which is something we never saw in the pre-targeted therapy era. Where the average survival was four to six months from the time of diagnosis to death. And now we're seeing many years.

Sarah Beatty:

What is that? I wonder what that, for a researcher like you were talking about yourself, what is that aha moment like? I wonder like, so many of us would go, "Oh gosh, we have 98 people who aren't responding. We have two that are, that's just an anomaly." But what is it about the researcher, the lung cancer researcher that goes, ooh, ooh, ooh, ooh. What about those two? Let's dig into those two.

Dr. David Carbone:

Yeah. Well, when you are a clinician, seeing these patients, you're not standing in front of an audience and trying to deal with a thousand patients at once. You have one patient in front of you and your job is to do the best job you can for that one patient. And it doesn't matter if you find an alteration that's present in two or five or 10% of people, and what matters is whether that patient has it. And if that patient has it's a hundred percent. And to me, we have to not only take things from mouse experiments and test them in people, but we have to learn from people about what the best mouse experiments might be. So, when I see my patient and they have an unusual response to a drug, the first thing I think is, is there some characteristic of that patient that I could try to figure out that might help, that I might look for, in other patients that could help match treatments to them and give them better outcomes?

Dr. David Carbone:

And so, I think it's a very satisfying aspect of being both a researcher and a clinician to see these patients and see the variability between patients and the variability from one person's cancer to another. And to understand the complexity in the laboratory of what drives a tumor and what makes one tumor different from another. And try to match those two and try to figure out the best treatment for not a thousand patients, not everybody, but that one person who's sitting in front of with kids at home and a husband, and suddenly been hit with this diagnosis. It's my job to figure out the best treatment for them.

Sarah Beatty:

Well, what it seems like, it's just the most impactful, meaningful puzzle solving that there could be is, making those connections and solving these life and death puzzles that you and many other researchers are doing. And I am so grateful that you've got that kind of mind to do that work.

Dr. David Carbone:

Well, these aren't subtle effects. Like I was saying, these are, if you can find that match in a prompt, period of time and implement it, like I said, these people can return to a normal quality of life. And from being in pain and short of breath and back to normal, basically. And that is something that we try to do with every patient.

Sarah Beatty:

Well, Dr. Carbone, thank you so much for your time today. I really, really appreciate it. Dr. Carbone has such a wonderful way of explaining complex terms so clearly. We're grateful to him for his time today. That's Dr. David Carbone, of the Ohio State University Comprehensive

Cancer Center. And you should know, he's just one of the amazing lung cancer specialists on LCFA's scientific advisory board.

Diane Mulligan:

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