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COMMENTARY

EGFR Mutations Are Not All the Same: the Importance of Biomarker Testing in Non-small Cell Lung Cancer (NSCLC)—A Podcast Discussion Between Patients and Oncologists

Stephen V. Liu · Ivy B. Elkins · Jill Feldman · Sarah B. Goldberg

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ABSTRACT

This podcast, for healthcare professionals (HCPs), patients, and patient advocates, is a discussion among a panel of two patients (and co-founders of the patient advocacy group EGFR Resisters, https://egfrcancer.org/) and two oncologists. The objective of the podcast is to explain the importance of biomarker testing for patients with *EGFR*-mutated non-small cell lung cancer. The treatment landscape for *EGFR*-mutated non-small cell lung cancer is evolving, and biomarker testing has become central to determining the best therapies for individual patients. The panel discusses what biomarkers are, the processes involved in obtaining biomarker testing, how biomarker information is used, and the importance of waiting for biomarker results prior to determining treatment. The panel also discusses patient perspectives on biopsy and biomarker testing and how HCPs can best help guide new patients through this process.

Keywords: *EGFR*-activating; *EGFR*-mutated; Biomarkers; NSCLC

Key Summary Points

What is discussed in this podcast?

Biomarkers in *EGFR*-mutated non-small cell lung cancer.

The importance of biomarker testing prior to treatment decisions.

Who is participating in this podcast?

The podcast features two patients (and co-founders of the patient advocacy group EGFR Resisters; https://egfrcancer.org/) and two oncologists.

The discussion may be of interest to healthcare professionals (HCPs), patients, and patient advocates.

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S. V. Liu (✉)
Division of Hematology and Oncology, Department of Medicine, Georgetown University Medical Center, Washington, DC, USA
e-mail: Stephen.Liu@gunet.georgetown.edu

I. B. Elkins
Patient Advocacy Group EGFR Resisters, Evanston, IL, USA

J. Feldman
Patient Advocacy Group EGFR Resisters, Deerfield, IL, USA

S. B. Goldberg
Division of Thoracic Oncology, Center for Thoracic Cancers, Yale School of Medicine, New Haven, CT, USA

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PODCAST TRANSCRIPT

Ivy Elkins: Welcome to our podcast discussion today. We will talk about how all *EGFR* mutations in lung cancer are not the same and why biomarker testing in non-small cell lung cancer is important. My name is Ivy Elkins, and I'm a patient living with lung cancer and a co-founder of the EGFR Resisters Patient Advocacy Group. I'll be talking to Jill Feldman, a lung cancer patient and advocate, also a co-founder of the EGFR Resisters.

Jill Feldman: Hi Ivy, thank you for having me. I look forward to the conversation today.

Ivy Elkins: Great. I'll also be talking to Dr. Sarah Goldberg, a thoracic oncologist from the Yale Cancer Center in New Haven, Connecticut.

Sarah Goldberg: Hi Ivy, it's great to be here.

Ivy Elkins: Great to have you and Dr. Stephen Liu, a thoracic medical oncologist from Georgetown University in Washington, DC.

Stephen Liu: Hi Ivy, thanks for having me.

Ivy Elkins: Fantastic. So, let's kick it off. We know that biomarkers are an important part of planning treatment for non-small cell lung cancer. Sarah, can you briefly explain what biomarkers are?

Sarah Goldberg: Sure. This is, I think, a somewhat confusing topic sometimes for people. The term is used to mean a lot of different things depending on the situation. The general way to think about it is that it's some form of a biologic characteristic that gives us some useful information about someone's cancer, in this case. You can use biomarkers in other things besides cancer, but for the purposes of this discussion, we're talking about them in cancer.

There are two main types of biomarkers, and this is where a lot of the confusion comes in. There are prognostic biomarkers and predictive biomarkers. Prognostic biomarkers can be thought of as how a patient potentially is going to do and what you can expect, regardless of the treatment. Predictive biomarkers help to determine whether a drug or some other therapy is more likely to be effective and if it's a good choice for that particular patient.

The most useful ones in lung cancer are predictive biomarkers: what can we know about the cancer, or about the patient, about the tumor, the characteristics that can help us decide what the best treatment for that patient is. That is a predictive biomarker, and examples of that are *EGFR* mutations. There is a lot of nuance which we are going to get into, but the first point is that a predictive biomarker will help you choose therapies.

Ivy Elkins: So, are any of these alterations, these biomarkers or mutations, inherited?

Sarah Goldberg: It's an important question and a lot of patients ask me this in clinic: "Is this something that I inherited from my parents, and can I pass this along to my children?" It depends on the biomarker we're talking about. In some situations, they can be inherited; in others, they are not.

In lung cancer, the vast majority of the biomarkers we're talking about, the mutations we're talking about, are not ones that are inherited. The reason for that is, when we talk about genetic alterations or mutations and such, there can be somatic ones, and there can be germline ones. The somatic ones are the ones that only occur in the cancer; every other cell in the patient's body does not have that alteration, just the cancer. You can't pass it along because it's only the cancer that has it, whereas germline alterations or germline mutations are in all of the cells, and those are the ones that are inherited and can be passed along. It varies from biomarker to biomarker, disease to disease, but in lung cancer, they tend to be somatic. There are some exceptions, but for the most part, that's what we see.

Ivy Elkins: Great, that's very helpful. So, how are these biomarkers in tumors identified?

Sarah Goldberg: It has changed over time. *EGFR* was one of the first ones we learned about, so we were testing for *EGFR*. We now know about a lot of different alterations. We've come from a place where we did single biomarker

tests. There are different versions of those; you can do single gene mutation tests; there are immunohistochemistry tests and FISH [fluorescence in situ hybridization] testing for certain alterations like *ALK* and *ROS1*.

More and more, we're doing next generation sequencing on tumors, for multiple reasons. Probably the main one is that you get a broad range of alterations from a single assay. A lot of the assays are now even including DNA sequencing, as well as RNA sequencing. You could get information on not just mutations, but also fusions and amplifications and other alterations. This varies based on people's practices, but we're tending to lean towards getting next generation sequencing to get this broad range of alterations, not just in one gene, but in multiple genes.

Ivy Elkins: Stephen, why is testing so important?

Stephen Liu: Great question, Ivy, and quite simply, it is critical to choosing the right treatment [1]. This has evolved a little bit over time, but we can't stress enough how important it is to perform proper biomarker testing and to do that testing right away. We cannot choose the best treatment, at any stage, for someone with non-small cell lung cancer without biomarker information.

In the past, we treated all lung cancers the same, because the only tools we had were chemotherapy. Now we know that lung cancer is not one disease; it is a family of related diseases. They have fundamental differences, and when we look at these differences at the DNA level, that dictates the biology of that cancer. It gives us information about patterns of spread, about prognosis, but most importantly, these DNA changes reveal different vulnerabilities. We're finally at the stage where we can leverage those differences into choosing the right tailored, personalized treatment.

It's relevant to anyone taking care of a patient with non-small cell lung cancer because they are pretty common. When we look at *EGFR*, estimates vary; it depends a lot based on where you are geographically and on some lifestyle factors, but approximately 20% of patients might have an *EGFR* mutation within their cancer [2]. Maybe half of patients with non-small cell lung cancer will have a known oncogenic driver [3], and our drugs are getting better and better.

So it (biomarker testing) chooses what path we go down in terms of our treatment. For advanced lung cancer, our treatment strategy is systemic therapy, and while chemotherapy ruled in the past, we now look more towards targeted therapy or immunotherapy. If we find a biomarker that we can act on, like an *EGFR* mutation or an *ALK* fusion, it directs us towards targeted therapy—often, pills with generally low-grade toxicities that are better tolerated than chemotherapy—drugs that we know will be effective. It also tells us that in that same group, immunotherapy will be ineffective. It guides us towards a treatment that will work and away from a treatment that won't work. If we don't have that information, Ivy, we're just guessing, and we don't want to guess. We want to get it right the first time.

On that note, it's also important not just to do the biomarker testing and to do the right type of biomarker testing, but to do it early. This is not a last resort, years down the line. This has to happen from the jump; while we want to get the treatment right at the beginning, it also impacts the safety of the drugs. We don't exactly know why this happens, but when we give targeted therapy after immunotherapy, the side effects are enhanced—they're a lot more dangerous [4]. If we want to give the right treatment at the beginning, we need the biomarker testing at the beginning.

Ivy Elkins: Thanks, Stephen. It sounds like biomarker testing really is incredibly important. Sarah, who should get tested and when?

Sarah Goldberg: For several years now, we've known that patients with advanced or metastatic stage 4 non-squamous, non-small cell lung cancer absolutely need to be tested. That's because most of the biomarkers, the mutations, the alterations that we find that we can act on, the ones that have a targeted therapy attached to them, are found in non-squamous, typically adenocarcinoma, non-small cell lung cancer. Those are the patients that we absolutely need to test at diagnosis. Ideally, we want to know that information before they start any treatment—and a lot of times, that is possible.

Patients often have to get imaging and may need radiation; before systemic therapy is started, and maybe even before radiation is started in some cases if it's necessary, we want to know the results of mutation testing. Stephen alluded to this; we want to get it right from the beginning. It's much better to give the correct treatment, the treatment that's most likely to work, rather than just start a treatment.

There are some situations where patients are really sick; they have a lot of disease, and they're very symptomatic. Testing can take some time, and there are situations where we do need to start chemotherapy while we're waiting for testing. But Stephen alluded to this; I try to not start immunotherapy before I know the results of mutation testing. That would really be something that you don't want to do. If someone has a targetable mutation, immunotherapy is the wrong choice for that patient, regardless of the PD-L1 status, which I know sometimes does direct us to immunotherapy.

What has changed in more recent years is our understanding that even some patients with squamous cell carcinoma can have alterations. Those patients tend to be light or never smokers. Sometimes, the histology is not so clearly defined and reports suggest squamous cell carcinoma, but it's not so clear. I think those patients should also get tested at diagnosis.

What has evolved is that now we have to start thinking about testing our patients with earlier stage disease, stage 1B, stage 2, and stage 3. We now have data specifically for *EGFR* mutation-positive lung cancer that (shows) we can use targeted therapies, specifically osimertinib, as adjuvant therapy after surgery [5]. We want to know the results, particularly of *EGFR* mutation status, in those patients ideally before surgery. While we're seeing the benefit of chemotherapy and immunotherapy for patients with early-stage disease before surgery, that may not be the right choice if someone has an *EGFR* mutation; so we need to know those results early.

I'll just name one other situation where we sometimes think about getting testing, and that's when a patient has been on a targeted therapy. We sometimes repeat molecular testing after disease progression. If someone is doing well on targeted therapy, and then they develop resistance and the tumor is growing, we sometimes think about a repeat biopsy and repeat testing in that scenario.

Ivy Elkins: Great, thanks. Now, Jill, I have a question for you. Do you sense that all newly diagnosed patients are actually getting testing?

Jill Feldman: That's a great question, because no, they aren't. As Sarah mentioned, it's indicated that people should be getting the testing because of adjuvant therapy specifically for *EGFR*-positive lung cancer. There was a chart review of 38,000 patients in the US Medicare system with newly diagnosed lung cancer that was actively managed. They found just about 50 percent of patients did not end up getting biomarker testing results before they started treatment [6], and it also included that biomarker testing wasn't ordered for some patients.

There was a smaller chart review study from the US community oncology group, and it reported similar findings. Only 46% of patients that were newly diagnosed had comprehensive biomarker testing before they started treatment [7]. I do want to note here that 90% of these patients got tested for ≥ 1 biomarker [7]. We need to test for at least the ones that have FDA-approved therapies, and there are many reasons that the testing doesn't happen.

It's important to note that only a small percentage of people are treated in an academic center. About 80–85% of people with lung cancer are diagnosed in a community or rural oncology setting and face a lot of medical disparities. It's certainly something that we need to work out.

Ivy Elkins: Thanks, Jill. Yes, I agree. This is definitely an area that can use some improvement. We've been talking about testing a lot. Here's a question for you, Sarah. How is testing done? Does testing have to use a tumor biopsy? What happens if a patient doesn't have enough tissue available to accomplish that?

Sarah Goldberg: I've certainly seen this in my practice many times where there's just not enough tissue to get what we need from the biopsy. But the nice thing now is, a couple of things have changed. Even with small biopsies, if you use an assay like next generation

sequencing, where you can get multiple genes tested in the same assay, it actually makes more efficient use of a small biopsy.

The other nice development in recent years that has completely changed the way that I treat patients, is liquid biopsies. This is something that is now part of my daily practice when I see people with lung cancer. I'm sending blood for ctDNA, or circulating tumor DNA, which sometimes people will call liquid biopsies. The idea here is that some cancers, not all, shed DNA into the blood, and you can pick this up in a blood test, which is pretty amazing. The technology has come so far that even small amounts of ctDNA are able to be detected in the blood.

This can be useful in a lot of settings. First of all, it helps when you don't have enough tissue. It also helps with turnaround time because it can take some time for tissue testing to come back at a lot of places, including my own. Blood-based testing, or these liquid biopsies, are sometimes faster. The one caveat here, I will say, is that if a liquid biopsy or ctDNA test does not show an alteration, the tissue biopsy is still critical, because not all cancers show up in the blood. It varies by the assay you are using. It can happen that the patient has a lung cancer that has a mutation, and it doesn't show up in the blood. Several studies have now shown that if you find it in the blood, it's real and you can act on it [8–10]. You don't need tissue confirmation of the mutation or alteration; if you don't find something in the blood, tissue testing is still important.

Ivy Elkins: Okay, great. Thank you. Stephen and Sarah, you've both said that it's best to get biomarker results before treatment starts. Sarah, how long does it usually take to get these results back?

Sarah Goldberg: It depends on what type of assay you're sending. It depends on where you're practicing, and if it's an in-house assay or if you're sending it out, because all these things just add time. The average in the US, and there have been some studies looking at this, is that it takes about 2 weeks [7]. You can rush testing, and I've definitely done that for patients where there's even more of an urgent need to get these results; sometimes companies are able to do that and expedite a bit, but it still takes time.

Again, one really nice thing about liquid biopsies is they tend to be faster, more like a 7- or 10-day turnaround time. Sometimes, we get the PD-L1 results back faster, in a day or two, and then we are waiting 2 weeks or sometimes more for mutations. But we wait, as long as the patient is stable and clinically it's okay to wait, because it's so important to get that information.

Stephen Liu: Yes, I agree with those timelines. I think that one of the big advantages of blood is that when I send blood, the testing is received by the lab the next day, whereas if we order tissue NGS (next-generation sequencing) and that tissue is not at my own institution, it sometimes takes a while to get the pathology department to ship it to begin testing. When this test is ordered, I think it's very important to just communicate with the testing group if it's taking a while, and to just check in.

Ivy, maybe I could ask you a question from a patient perspective. How hard is it to wait for those biomarker results?

Ivy Elkins: It's really very hard to wait. As a patient, you're getting this biomarker testing done at a very vulnerable, stressful time. It's either when you were first diagnosed with lung cancer or at a time that you've just found out from your oncologist that your lung cancer is progressing. You are already so anxious about what kind of treatment is going to be available for you and what your life is going to look like going forward; then you find out that you can't even start on any treatment right away. You have to wait to get the results of a test back, and it could take 2 weeks, give or take a little bit.

It is something that is very stressful to hear at that point; you just want to get started doing something once you know that there's some cancer that's active in your body. You kind of get nervous that the cancer is going to grow while you're waiting, which isn't very likely to be that significant, or are nervous that you're sitting around doing nothing while something should be done. It is a very hard situation to be in as a patient, and communication is key in terms of why this is a requirement, and why the wait is a requirement.

Stephen Liu: I think that's a good point. Jill, do you have any tips about how to make that process a little bit easier?

Jill Feldman: I agree with everything Ivy just said. I would add just a few things. And one thing that I would add is, you know, at a time when you completely lose control of almost everything, of your life, the one control that patients want is to be able to have a plan. Yes, it's important they understand why you need to wait for biomarker results, but clinicians or nurses need to understand that this is happening at a time when anxiety and distress stop your ability to be able to comprehend things clearly.

And it's also important to acknowledge the anxiety, because as patients, we feel like, oh, it's so nonchalant, the results will be back in a few weeks, and then we'll start treatment—after you get approval from insurance, which can take time as well. So, there are so many factors and I think, you know, kind of acknowledging the stress is critical.

As patient advocates, Ivy and I talk to patients a lot, but I think it would be even more helpful if their doctors and nurses could take a minute and explain it all to them.

Stephen Liu: Sarah, on that note, do you have any advice as to how you approach this situation with your own patients?

Sarah Goldberg: I think the things that I've found to be helpful are that I try to explain that and give the bigger picture of waiting 2 weeks is very unlikely to change anything. But starting with the wrong treatment can. The other thing I've found that's helpful, especially when I think the result is going to be 2 or more weeks, is seeing the patient back even before the results come back. Now with telemedicine, that's even easier, but just checking in, like, "We're watching you. We're keeping an eye on things. We're making sure nothing bad is happening while we're waiting. We're answering questions that you thought of the day you left the office and forgot to ask."

Stephen Liu: I think those are good tips, and I often say we're not looking for the fastest treatment, we're looking for the best treatment, explain why the stakes are so high and not just dismiss it, and really acknowledge and appreciate that anxiety. I think the check-in is really important. What about the discussions about biomarkers in general? I think that because there's a lot of science involved, I worry that sometimes the language isn't appropriate. Sometimes there's maybe too much detail, sometimes not enough detail.

Ivy, could you talk about what biomarker testing discussions are like between a patient and healthcare provider and maybe what they should be like?

Ivy Elkins: Yes, all too often you have a short amount of time for your appointment with your healthcare provider, especially when you've first been diagnosed or you have progression, and there's so much that needs to be covered. And then biomarker testing is often kind of dropped in at the end of the discussion. Many patients have never even heard the term "biomarker testing" prior to having a diagnosis, and lots of terminology is out there that goes into explaining what biomarker testing is, mutations and alterations and genes and DNA.

So, the discussion about biomarker testing really should be as clear and as simple as possible. What is being tested for, explaining terminology that might need to be explained, and what options might become available based on the testing. Also just make it clear why the wait is necessary, what happens, and why it takes such a long time, because it's hard for patients to understand that as well.

I think explaining to a patient that there is a long wait because the process is involved in order to get the right answer is very important. It should also be allowable in the time given for patients to be able to ask questions about anything that is confusing to them, whether they can do that with their oncologist or through a follow-up with an oncology nurse.

Stephen Liu: These are great points, and this is a very important conversation that is often happening the first time an oncologist is meeting a patient. And this patient may have no experience with cancer, with lung cancer, with any of the terms we're using. Jill, do you have any advice for a healthcare provider about how to approach this big topic in a limited amount of time?

Jill Feldman: I use the analogy of what it feels like to be diagnosed with lung cancer. Imagine that you're going about your everyday life and all of a sudden you are drop-kicked into a foreign country. You don't know where you are. You don't speak the language or understand the culture. The terrain is unfamiliar. You don't have a map, yet you need to figure out how to survive while confronted with all these decisions, knowing there's no room for error, but really trying to understand the risks versus the benefits, all while a mountain lion is chasing you.

And that's really, truly where patients are, at a time when anxiety and distress cloud your ability to think clearly. The most underrated skill of someone in oncology, a doctor or nurse, is the ability to communicate with patients and families at one of the most frightening times in their life, and really building that trust is critical.

Patients and families want to know that the person taking care of them also cares about them. While you still have anxiety, you at least feel like you're in good hands and can trust what your doctor or nurse is saying.

Stephen Liu: These are such great analogies, great points. Sarah, what has your experience been with having these types of discussions with a patient that you've just met?

Sarah Goldberg: It is how to communicate that. It's something that I think we learn when training and we fine tune as we see how things impact patients and how they are understanding things. I learn from my patients every day on how they take in the things that I say. But I really think trying to use straightforward language, explaining things in ways that patients understand. People are going to look online and read about things. So, they might as well hear from us the way that we understand things and we think is important and relevant to them.

Stephen Liu: Yes, there are some great resources online as well, but your point about learning and adapting, finding out what works—patients learn in different ways, they understand in different ways, so, you need to be able to adapt. If you're talking about something in a very scientific manner, you can pick up that this is kind of going over someone's head. You might need to start over, and you shouldn't be afraid to do that. Or if you're explaining it in very simple ways, but that patient really wants that scientific breakdown of what specific mutation is there, you should be able to offer that.

So, we have to adapt, and one of the biggest things I've learned over the years is just repetition, that I can't expect the patient to remember everything I deliver in that first visit. It's too much. So, at that second visit, I'm going to repeat a lot of the stuff I said that first visit, and probably the third visit and the fourth, because recall is very tough when you're in that situation.

Ivy Elkins: I totally agree that repetition is very, very important for patients. The more often we hear about something, the more it's easier to say and remember and comprehend. Speaking of terminology, a mutation-positive lung cancer as a diagnosis isn't something that most patients have heard of. Stephen, what does it mean if you get that diagnosis?

Stephen Liu: EGFR stands for epidermal growth factor receptor, and this refers to a specific gene or a part of the DNA, and in the context of lung cancer, we're really talking about a mutation. We're trying to move away from vague terms like "positive" or "negative", and really the details are important.

In lung cancer, what matters is not the expression of *EGFR* but the mutation status. EGFR plays a role in the development of normal tissue, but it can play a role in the growth of cancers. And if a cancer is relying on that signal to survive, blocking that signal can prevent that cancer from surviving, and that can be an effective cancer treatment. So, we devised these EGFR inhibitors. We'll refer to them as tyrosine kinase inhibitors. These are typically pills. We first tried these years ago as a treatment for all patients, and as sort of a salvage treatment. But as time went on, it became very clear that this was only working for the patients whose cancer had an *EGFR*-activating mutation, and for patients whose cancers had nothing with regard to *EGFR* mutations, the drug was no better than the placebo.

When we have an *EGFR* mutation test result, it tells us that EGFR inhibitors will generally work. Now, lung cancer is not a situation where

we can make promises or guarantees, but when we see these test results, we have confidence that the right treatment is an EGFR inhibitor.

In the days when we were using chemotherapy alone, the chance of chemotherapy significantly shrinking a cancer was probably on the order of about 25–30% [11]. So even though it's a treatment we associate with lung cancer, it didn't really work all that well, whereas with an EGFR inhibitor, the vast majority of patients will get benefit from these medicines [12, 13].

Early generations of the drugs, first- and second-generation inhibitors, compared to chemotherapy, were more likely to work, so they had a higher response rate [12, 13]. They were more likely to work for longer and to prevent that cancer from growing, so they had a better progression-free survival [12, 13]. Now, we have third- generation inhibitors, and these have shown pretty consistent high response rates. They are effective in the brain, which is an important area of control for these types of cancers, and these were compared to first-generation inhibitors and they actually did show a survival benefit [14]. It's difficult to prove that a third-generation inhibitor has a survival benefit over chemotherapy in studies, but I do think that if patients did not receive these agents, they would not live as long, so this would be considered our global standard of care.

The most common *EGFR* mutations are exon 19 deletions and exon 21 L858R point mutations [15]. There are others, and we're getting a little smarter about how to decode all the background mutations and how they should impact treatment.

Ivy Elkins: Thank you, that's very helpful. So, given that there are different types of *EGFR* mutations, Sarah, when a testing report comes back and shows that there is an *EGFR* mutation, how do you interpret those results?

Sarah Goldberg: Years ago, it used to just be an *EGFR* mutation is present. But as Stephen mentioned, it's more complicated now. Typically, the reports will come back with a specific type of *EGFR* mutation. They sometimes will say exon 19 deletion or L858R point mutation. Those account for about 90% of cases, but even within specifically the exon 19 deletion category, there are a lot of different exon 19 deletions [15]. It is critical to know which *EGFR* mutation we're talking about, and because it's not always so straightforward, I find myself often talking to our molecular pathologist. Do we know that certain EGFR inhibitors might be better for that mutation, or another EGFR inhibitor? So, it sometimes is important to discuss findings of these reports with a molecular pathologist.

The other thing that's sometimes complicated is that very often, tumors don't just have one alteration. Sometimes you can have two *EGFR* mutations in the same tumor. It can be very complicated. Those are situations where I sometimes will talk to a molecular pathologist or go to the literature and see what has been found in what's called compound mutations, when you find multiple mutations in the same tumor, and that can be really helpful.

Ivy Elkins: It sounds like it could be very confusing. Stephen, could you go into just a little bit of detail about how certain treatment decisions may be influenced by finding specific *EGFR* mutations?

Stephen Liu: Sure. This is a moving target, and we're getting new drugs on the horizon, so this is likely to change, but I think the overall message is that the specific *EGFR* mutation is going to dictate which agents are going to be best used. In the US, for the common mutations Sarah outlined, exon 19 deletions and L858R point mutations, we have five different oral EGFR tyrosine kinase inhibitors that are FDA-approved: osimertinib, which is the only third-generation (agent that is FDA-approved in the US) and generally the preferred first-line agent, the first-generation agents, erlotinib and gefitinib, and the second-generation agents, afatinib and dacomitinib. And that first-generation agent, erlotinib, can also be combined with ramucirumab, which is an angiogenesis inhibitor that is an approved regimen in the US.

Now, these common EGFR mutations, exon 19 deletion and L858R point mutation, respond well to these agents, but they are different. An exon 19 deletion does have a better prognosis [12, 13, 16], and if we look at the studies with osimertinib, for example, the benefit was greater with the exon 19 deletion than with the

exon 21 point mutation (L858R). They would be treated the same today. We'll see if that changes in the future.

For the atypical mutations like S768I, L861Q, G719X; afatinib, which is a second-generation inhibitor, is an FDA-approved agent—although there is a lot of data for osimertinib with many of these mutations [17–19].

The *EGFR* exon 20 insertions do not respond well to immunotherapy, and also did not respond well to the other standard EGFR inhibitors [20]. So, we're using only chemotherapy there, which is very frustrating. Fortunately, we do have two relatively recently approved agents in the US: mobocertinib, an oral agent, and amivantamab, which is an IV infusion, are both approved specifically for EGFR exon 20 insertion [21].

Now we've got a lot of drugs in development, and a good option at progression, maybe even at diagnosis, would be a clinical trial, so it really is worth discussing all the newest agents with an oncologist, but again, the details here matter. We can't just say *EGFR* is present; it has got to be the specific mutation that's going to tell us what the best drugs are.

Ivy Elkins: Thanks, Stephen, thanks for the detail. Question for both of you, Sarah and Stephen, can you both explain why further biopsies might be indicated after a patient's treatment has started?

Sarah Goldberg: This is an interesting aspect of EGFR therapies and other targeted therapies, too. After treatment with an EGFR inhibitor, as Stephen mentioned, typically osimertinib is the drug that we start with for the common mutations, we know that the tumor can change. We could see new mutations show up in *EGFR* or in other genes. We can see other alterations, like amplification of different genes, of *EGFR*, and other things. And the other rare, fortunately, but important thing to know is, sometimes, the cancer can change type. So, you start out with an adenocarcinoma, you give an EGFR inhibitor. At the time that the cancer starts to grow again, if you get a biopsy, you might see that there's a transformation to a different type of cancer such as small cell lung cancer or squamous cell carcinoma. These are things that we don't fully understand.

There's a lot of work going on into how these things happen, but the only way to know about them is to get a biopsy, so it has become standard practice to reassess the tumor at the time of progression on an EGFR inhibitor. There's a bit of debate about how you do that. Do you get a new biopsy, do you get a liquid biopsy with ctDNA, should you do both? A nice benefit of a liquid biopsy is you don't have to go through a procedure, but the tissue will tell you about those transformations to small cell or squamous cell cancer that are important. I always send a liquid biopsy when a patient is progressing on an EGFR inhibitor, and I also consider getting a tissue biopsy either at the same time or if the liquid biopsy doesn't show anything useful. They can be complementary to finding out what's happening in the tumor.

Typically, you still see the baseline *EGFR* mutation that was there before, but you might see additional alterations. The question comes up, what do you do with that information? You know, it's a really amazing phenomenon that this happens, but is it useful information?

Well, it actually can be. There's a lot of data now that shows that additional targeted therapies may be useful. We don't have any FDA approvals for those, but there's a whole lot of studies now that are looking at *MET* amplification after progression on an EGFR inhibitor, then targeting *MET* might be a useful strategy. You see what has come up at the time of resistance, and then see if there's a clinical trial that specifically is looking to address that alteration or that issue in the tumor. I think that is an important aspect of treating people who have *EGFR* mutation-positive lung cancer.

Stephen Liu: Yes, just to build on what Sarah said, we want to try to understand resistance. And when we give an EGFR inhibitor and it works well, patients will feel better, sometimes within days, we'll see these dramatic responses. We also know that it's not a cure, and at some point these cancers can evolve and figure out ways to grow. If we continue the same medicine and it works really well, and then one day, it stops working, that means that the cancer has somehow changed. And if we can try to better understand how it has changed, maybe we can

tailor the next line of treatment to make it a little more likely to work.

This was really how we first started using osimertinib. When we think of the first- and second-generation EGFR inhibitors, like erlotinib, gefitinib, afatinib, dacomitinib, when we would give those agents and they would stop working, about half the time, it was because a new *EGFR* mutation emerged called T790M. In that setting, that would not impact the binding of osimertinib, and that was how osimertinib was first approved as an option for patients who had this T790M resistance mutation.

If we try to understand why this cancer is allowed to grow, what is it using to survive, we can try to take that away with combination therapy. Dr. Julien Mazieres presented the INSIGHT 2 trial at ESMO '22—the trial showed that when we add a *MET* inhibitor, in that case, tepotinib, to osimertinib, it worked about half the time, and for half the patients, it worked for at least 6 months, maybe even more [22]. We have to think about what are the toxicity and financial implications of adding a second agent, but we're trying to tailor next-line therapy based on the specific type of resistance.

Now, just to quickly acknowledge, while we'll say biopsies are something that we try to do often, we also want to note that it is sometimes difficult to get a biopsy, and our colleague, Dr. Zofia Piotrowska at Mass General Hospital, led the ELIOS study, which just looked at biopsies at progression. While the focus of that was understanding resistance, if we look at the early point, only about 39% of patients on that trial for repeat biopsies actually got a repeat biopsy [23]. So even under perfect circumstances, it's difficult sometimes to get these repeat biopsies. That's why liquid biopsy can be so helpful.

Sarah Goldberg: I will just add that if you get another biopsy, a tumor biopsy or a liquid biopsy, and you find an alteration, thinking about how to act on that, but a lot of times we don't find anything. You might find the original *EGFR* mutation, but sometimes we don't find anything targetable that's developed as a mechanism of resistance. So, in those situations I often am thinking about a clinical trial. But the other option is chemotherapy. We typically use an EGFR inhibitor as upfront treatment in someone who has an *EGFR* mutation-positive lung cancer. So typically, then, if there's not a trial available and I don't find a targetable alteration, I'll think about giving chemotherapy, and that can sometimes work really well for patients as well.

Ivy Elkins: Great, thank you. Speaking of repeating biopsies upon progression, Jill, you're in contact with a lot of patients. How do you feel that patients feel about these repeat biopsies upon progression? Do they tend to be receptive to the idea?

Jill Feldman: I think when it comes to repeat biopsies, patients now understand why the biopsy is so important, and so they are more receptive to the repeat biopsies. It doesn't change the fact that there is still a burden, a psychological distress, and patients have to take time off work. I mean, you could have a pneumothorax. There's a lot that can happen when you biopsy, especially the lung.

It's not necessarily an easy decision, but patients are definitely more receptive to it. They have to understand what the potential benefit is of doing this, and hopefully, I feel most of them will have had the discussion with their doctor already about this. We don't know if it will provide information; if it does that and there's an approved drug that targets what we found, then we'll look to go that way. On the flip side, we may find something, but there's not an approved drug and, as Sarah mentioned, we'll look at a trial.

The problem is, a lot of times patients don't necessarily qualify for trials and that's really stressful for a patient—to know they can't get into the trial. It's something that again comes back to communication and to have these things addressed up front. That and making sure that insurance will cover it—sometimes, that's an issue as well. So, if there's an opportunity to do ctDNA sequencing first, knowing that a tissue biopsy would still be covered, then that would definitely ease a little bit of anxiety, getting those results back earlier.

Ivy Elkins: Thanks, Jill. There's definitely a lot of things to be considered. Okay, I have one final question for Sarah and Stephen. What do you see as the future direction of biomarker

testing and treatment in *EGFR* mutation-positive non-small cell lung cancer? Sarah, we'll start with you.

Sarah Goldberg: I think that we've seen so much progress and we've seen the benefit of great drugs, but it's the biomarkers that are helping us to fine tune how we're using those drugs and to make them work even better by finding the right patients to use them in. So I think that in the future, we're going to hopefully be seeing more of that, where there are amazing drugs that are in development for *EGFR* mutation-positive lung cancer, and how we sequence them, if we think about combinations, if we use them first, if we use them second, if we combine them initially, I think all of those things will be fine-tuned by the biomarker.

I don't think there's going to be a one-size-fits-all. I think the biomarker will help to define what the best strategy is within *EGFR*-mutated lung cancer. It may be that a cancer with the specific mutation benefits most from this therapeutic strategy, whereas this other mutation, again within *EGFR,* might benefit from another. I think that is hopefully going to be part of the future of biomarker testing, fine tuning the selection of treatments based on the specific *EGFR* mutation or co-mutation that we find in the cancer.

Stephen Liu: Yes, I agree with that. I think that within each *EGFR* mutation, there are a lot of differences with the other mutations that exist with the specific type of exon 19 deletion, for example. When we look at the horizon with the antibody drug conjugates, with chemotherapy, with newer inhibitors, there are some people that are going to do really well with just osimertinib, but there are others that are not going to do as well, where we might see early resistance, and it would be nice if we could tell upfront who's not going to do as well with osimertinib, who maybe needs a little more of an aggressive treatment or combination therapy, and I think that further refinement is where we're going. But in the immediate future, Ivy, I'd be happy if just everyone got this testing, because I think we have a long way to go just with the basic testing in this country.

Ivy Elkins: Yes, I agree, that would be my wish for the coming close short-term future is to get everyone the testing that can help direct their treatment. I would love to see that.

Thank you all so much for being part of this podcast discussion. I think we have covered a wealth of important topics and we appreciate your participation.

Jill Feldman: Thank you.

Sarah Goldberg: Thank you so much.

Stephen Liu: Thanks, Ivy.

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