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### Exploring EGFR Mutations in Lung Cancer: Key Diagnostic & Management Strategies

Dr. Sands:

Detection of EGFR mutations and effective therapy has been one of the biggest advances in lung cancer treatment, which is why today we're going to explore current and future treatments for these mutations. Welcome to *Project Oncology* on ReachMD. I'm Dr. Jacob Sands, and here with me today is Dr. Pasi Janne, a professor of medicine at Harvard Medical School and a translational thoracic medical oncologist at the Dana-Farber Cancer Institute. He's also director of the Lowe Center for Thoracic Oncology, and the scientific co-director of the Belfer Center for Applied Cancer Sciences. Dr. Janne, welcome to the program.

Dr. Janne:

Thank you very much. Happy to be here.

Dr. Sands:

So, Dr. Janne, let's start with testing. I've heard of various different ways of testing and different technologies. How are you evaluating patients when you first see them, and what can you speak to the testing for EGFR mutations?

Dr. Janne:

So, there are really a couple of different ways of doing genetic testing from an individual's cancer. The best way is to do it directly from the tumor specimen, and today in 2021, testing should really be part of a larger panel of genes that are being tested, not just for EGFR mutations, but for many of the other genetic alterations where we, at the moment, have regulatory approval for specific targeted therapies. In addition, of course, tumor testing allows you to look at things, like histology and protein expression. On the other hand, I recognize that it's not always feasible to do testing from specific tumors, hence there has been technology that's been developed to be able to test from the blood, as cancer has spilled the genetic information into the blood. This is typically successful seven out of ten times, and so if you do a testing from the blood and it's completely negative, I think that should reflex one to go back to the tumor. But it is an alternative that many of us have come to use.

Dr. Sands:

And then we hear about PCR and NGS and the timing that it takes on these different ones. Are there times where you'll order one, or do you generally go with NGS? Are there times then that you'd use PCR or some of these other, more pointed tests?

Dr. Janne:

Yeah, timing is fairly an issue and we want testing to be as rapid as possible because we need to use it for patient care decision-making. Typical NGS sequencing takes about two weeks to complete from the time of receipt of the specimen, and sometimes that's too long of a period of time. There are tests that one can do – so, for example, EGFR testing can be done as a singleton test, meaning that it's testing just for the EGFR mutation. And there are rapid assays to do that, that can take only 24 or 48 hours to complete. But in general, if one can wait, the panel-based testing is better because you will not only test for EGFR, but you will test for everything else simultaneously.

Dr. Sands:

Now for those results of EGFR mutations, there's a term that's often used at first: sensitizing mutations. Can you speak a little bit to what "sensitizing mutations" means, and if all EGFR mutations are treated in one way, or if there are certain ones to point out?

Dr. Janne:

Sure. I would think about EGFR mutations as three major buckets. There are the common EGFR mutations, the exon 19 deletion and

L858R mutations, which are the ones that we typically think about as the most sensitizing mutations. It is the one for which the regulatory approval exists for all of the various EGFR inhibitors, and the ones that are typically tested in the front line setting for clinical trials. The second bucket would be your atypical EGFR mutations. These are the ones that are in exon 18, like G719 mutations or exon 21 L861Q. These are about five to ten percent of EGFR mutations. Afatinib is the only drug with regulatory approval for this subset of EGFR mutations. And finally, there is the rare category – again about five to ten percent of the EGFR exon 20 insertion mutations – this is a family of mutations. There's at least 15 different ones that span this region in EGFR exon 20. And despite being EGFR mutations, they are not ones where we currently have a drug that is approved for this particular subset but is one where there's an active effort of finding a drug that would also work in the patients, or specifically in the patients that have the EGFR exon 20 insertions.

Dr. Sands:

So, if we now focus on treatment, let's discuss the most common of the sensitizing mutations: L858R, exon 19 deletion – what is your preference for first line treatment? Because there are multiple different treatment options that are approved. What's your preference to this?

Dr. Janne:

Well, there are multiple ones that are approved, but I think the vast majority of what's being used in the U.S., and certainly my own preference, is to use osimertinib as the first line therapy. It's associated with an improvement in not only progression-free survival, but overall survival, compared to prior generation EGFR inhibitors. It can penetrate the brain quite well, and so for patients that present with brain metastases, it's an effective way of treating them instead of with radiation, and it tends to be better tolerated than the prior generation EGFR inhibitors. So, as I said, in the U.S., that has migrated into the first line setting for patients with newly diagnosed advanced EGFR mutant lung cancer.

Dr. Sands:

Now, I've heard people make the argument that there are other EGFR directed therapies that would still potentially be something that they could use in the first line and save osimertinib for later on. What is your response to those arguments?

Dr. Janne:

I think that argument comes from the situation that when osimertinib was first developed, it was developed against the most common resistance mutation to prior generation EGFR inhibitors, the EGFR T790M mutation, which happens about 50 or 60% of the time to prior generation inhibitors. I think the challenge is several-fold. One is that we're not smart enough to figure out who's going develop the T790M resistance mechanism versus something else, and so to say, just start with the prior generation drug with the hopes of developing T790M resistance, it may happen, it may not happen. I just don't know that we can predict that. Second is that you may not always get to second line therapy. Sometimes patients decline and you don't get to second line therapy, and aren't able to treat it with a drug like osimertinib. And I think some of those arguments have changed since the overall survival benefit of osimertinib. You know, now it has an overall survival benefit compared to prior generation drugs. It would be not in the patient's best interest to receive a drug that had an inferior survival benefit. I think my own approach, not only to EGFR inhibitors, but to any therapy, is to use your best drug first. There's no reason to save it for later, because not everyone makes it there.

Dr. Sands:

For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Jacob Sands, and I'm speaking with Dr. Pasi Janne about treatment options for EGFR mutations. So, continuing our discussion about treatment options, you've mentioned osimertinib in the first line setting. When patients have progression, at that point what are you doing?

Dr. Janne:

Well, I think we now understand that progression is not a one-size-fits-all process. It's actually quite heterogenous. There are many different ways in which cancers can develop progression to osimertinib. Some of those ways are targetable, and for some of those ways, we have effective therapies or subsequent therapies. And so, it's important to recognize or understand, what is the progression? What's happened to the cancer? And again, here a repeat biopsy is the preferred method, of evaluating that because not only will that allow you to have a tumor available for sequencing, but it allows you to look at it under the microscope and ask, did small cell transformation or squamous cell transformation, which have been seen as resistance mechanisms to first line osimertinib. You know, those would dictate, a very different type of therapy. I think if you are then able to sequence it, you look for the targetable alterations, secondary EGFR mutations, that are unique resistance mechanisms to osimertinib. Other pathways can get activated – MET, HER2, others which we can add a targeted therapy or evaluate that combination in a clinical trial setting. So, I think it's important to recognize or understand why or what is happening in the cancer, in terms of resistance, because that may lead you down different pathways.

Dr. Sands:

So, let's get into some of the research pipeline and looking ahead. First, we'll start with progression. Start with the setting of progression

after first line therapy, so things like HER3, for example. Are you able to explain a little bit about HER3, and the expectations around that? And maybe some of the other studies that are being developed?

Dr. Janne:

Right. So, the HER3 is the HER3 antibody drug conjugate. And here we're leveraging the knowledge and the biology of EGFR-immune cancers, in that EGFR-immune cancers also tend to express HER3, which is one of the other EGFR family members. HER3 is not osimertinib or any other EGFR inhibitor resistance mechanism. It just comes for the ride, it's used for some of the biologic functions of EGFR-immune cancers. And so, the HER3 antibody drug conjugate leverages this expression and uses it as a Trojan horse, in a way, to deliver a toxin, a chemotherapy-like molecule, specifically to cancers that express HER3, like EGFR-immune cancers. And so, in the studies to date, there's definitely been activity. There's been responses in patients that have failed, osimertinib or other multiple EGFR inhibitors. And I think one important feature of the treatment is that since it's not specific to a mechanism of EGFR inhibitor resistance, it works broadly across multiple different resistance mechanisms, or even in cancers that do develop resistance to osimertinib and you go through the exercise of sequencing them and you find nothing targetable, or nothing at all. It looks exactly like the pretreatment cancer, except it's clinically resistant. It still can work in that situation. So it is kind of a broader approach to treating resistance, and again, leverage is a unique feature of EGFR-immune cancers. Now, there are other antibody drug conjugates out there that have also seen responses in EGFR-immune cancers, like the S1062A and other antibody drug conjugate, this time against a protein called TROP2, also often found, expressed in cancers. So, I would say that's one approach. Then the second approach that's being tested clinically is going after the specific resistance mechanism. So, targeting MET amplification with a combination of an EGFR inhibitor and a MET inhibitor, or targeting EGFR mutations that can happen as a resistance mechanism to osimertinib. Many of those resistance mutations, or cancers with those resistance mutations to front-line osimertinib still are sensitive to prior generation EGFR inhibitors, and you can switch someone often to one of those EGFR inhibitors, and still achieve a clinical benefit afterwards. And so there's a lot of interest in trying to understand or develop a strategy for cancers that develop progression, and my thought here is that it's not going to be a one-size-fits-all. It's going to be tailored a bit depending on what the actual mechanism is.

Dr. Sands:

And now looking forward in the first line setting, is there anything that you find particularly intriguing, as far as first line trials?

Dr. Janne:

Yeah, I think one of the things that I think all of us recognize is that although an EGFR-immune lung cancer is a good example – that, you know, although, single agent therapy has been quite effective – it ultimately has its limitations, and the question is, how do you improve upon that, and where do you improve upon that? And first line therapy is certainly one potential option. Now, prior to having osimertinib, when one tried to do combination trials with drugs like afatinib or erlotinib, it was pretty difficult, due to toxicity. And so I think osimertinib has opened some of those doors that were previously closed as well. There's a lot of interest in anti-angiogenesis combinations trials. There's data on prior generation EGFR inhibitors, with bevacizumab and ramucirumab, showing improvement in progression-free survival. Whether that same thing applies to osimertinib, that is currently being tested. There is targeted therapy combinations, EGFR-TKI combinations, such as with osimertinib and gefitinib, because again, some of the osimertinib resistance mechanisms are sensitive to gefitinib, and if you treat with both drugs simultaneously, you may be able to prevent that mechanism or resistance from happening in the first place, as well as targeting it further downstream with drugs like MEK inhibition.

I would say the biggest surprise over the last few years has been the re-emergence of chemotherapy in this space. When EGFR inhibitors were first developed, without much understanding of the current biology that we understand, they were tested together with chemotherapy in broader patient populations, and had absolutely no benefit. And subsequently, even after EGFR mutations were identified, smaller studies were done that really didn't seem to suggest that adding chemotherapy to a drug like erlotinib did anything more than erlotinib alone, except add side effects. But over the last couple of years, there've been a few studies using now modern chemotherapy: carboplatin and pemetrexed with maintenance pemetrexed, studied from Japan; and a second study from India that added that chemotherapy to gefitinib, compared to gefitinib alone had dramatic improvement in progression-free survival and overall survival in both studies – sort of re-introducing the idea of, well, does chemotherapy now add to an EGFR inhibitor, or modern chemotherapy add to an EGFR inhibitor compared to an EGFR inhibitor alone? This has now been extended to osimertinib.

There's an ongoing trial called the FLAURA 2 trial, whereby carboplatin or cisplatin and pemetrexed is being combined with osimertinib versus osimertinib alone, to ask the question, "Does chemotherapy add in this situation as well?" Something that we'll hopefully know in the next couple of years.

I think the other thing that is going to also evolve, kind of similarly, as we think about the combination therapies is this concept of who actually needs a combination therapy. We know that if you start in the FLAURA trial – in the front line osimertinib trial, at three years, 28% of the patients who started on osimertinib were still on osimertinib. I would love to be able to identify those 28% of patients from the beginning, and say, "You have a good prognosis, EGFR-immune lung cancer. You'll do fine with osimertinib, for multiple years." And at

the same time, identify the individuals who have progression, either at the median or even sooner than the median, despite having the same EGFR mutation. They may have high risk cancer, however defined, and maybe these are individuals who need a more intensified therapy – the chemo combos with targeted therapy combos. I think that's an aspirational goal. I don't think we're there yet, but hopefully, we will get there at some point.

Dr. Sands:

Well, in a field that's fairly recent with EGFR mutations, it is exciting to hear about so much on the horizon as well. With that, I also want to congratulate you now on having the EGFR center there. I'd like to thank my guest, Dr. Pasi Janne, for joining me to discuss treatment options and testing for EGFR mutations. Dr. Janne, absolutely wonderful having you on the program.

Dr. Janne:

Thank you, my pleasure.

Dr. Sands:

I'm Dr. Jacob Sands. To access this and other episodes in our series, visit [ReachMD.com/ProjectOncology](https://ReachMD.com/ProjectOncology), where you can be part of the knowledge. Thanks for listening.