



## Q&A Session with Dr. Lecia Sequist, following presentation on Acquired Resistance to EGFR TKIs, and Data from Re-Biopsying Lung Tumors Over the Course of Treatment

**Dr. West:** I'm Dr. Jack West, President & CEO of GRACE, the Global Resource for Advancing Cancer Education.

Here's the question and answer session following the presentation by Dr. Sequist, Assistant Professor of Medicine at Massachusetts General Hospital and Harvard Medical School in Boston, Massachusetts. Dr. Sequist spoke on acquired resistance to EGFR tyrosine kinase inhibitors and the possibility of repeat tumor biopsies over time. She covers several questions offered in advance of her presentation, followed by a live Q&A component.

This program is offered by GRACE, the Global Resource for Advancing Cancer Education, in partnership with the LUNGeVity Foundation.

**Dr. Sequist:** Before we turn it over to any questions from people that are logged into this webinar, Dr. West had asked me to give my opinion about a couple of questions. I'll just give you my opinion, because there's no data.

*Are there ways to postpone resistance to erlotinib?*

The answer is, we don't know. There are certainly a lot of studies that are on-going that look at randomizing patients to Tarceva versus Tarceva plus fill-in-the-blank. And the whole goal of studies like that is to see if whatever drug is in the fill-in-the-blank can postpone resistance to erlotinib (Tarceva). So, some of those were the trials that I listed before. There's looking at HDAC inhibitors, looking at HSP-90 inhibitors, HER-3 antibodies. I think there are some trials using an anti-IGF treatment. So, there's lots of things that are under study, but so far nothing has been shown to be able to do this yet.

*If you do progress on erlotinib (Tarceva), should you come off of that drug at the time of progression or stay on it?*

Again, there's no data about this, other than there is one trial that's been published by Memorial Sloan Kettering. It wasn't exactly this situation, but they did show that a small number of patients that did have an EGFR and then came off of Tarceva while they were being monitored. There was an increased flare in their tumor activity on a PET scan. So in other words, they had a PET scan when they were still on the Tarceva. Then they came off of the Tarceva and had another PET scan that was hotter than the one that was just a few weeks before. That, along with clinical experience of doctors seeing patients having an acceleration in the growth of their cancer has made a lot of people excited about this concept of maybe just staying on erlotinib at the time of progression and

adding other things to it. Maybe things like Avastin or other chemotherapies, pemetrexed.

So this is actually being done quite a bit in practice. There are many patients who are on say something like Alimta (pemetrexed), together with their Tarceva. I have seen this strategy work very well in a number of patients. But there's really no data behind that.

I think there is a down side to potentially staying on the Tarceva. That is that we know that if you have a holiday from Tarceva, you can regain sensitivity. This has been reported in a number of different case studies. I think we've all seen patients like this. They came off of Tarceva. They cycled through a number of different therapies and then, after a year or more break with no EGFR inhibition, they circle back to the Tarceva. They try it again and had another good response.

In some cases, that can last several months. Often it doesn't last as long as the first response. But it can be an actual durable response. There has been no study comparing these two strategies head to head: whether to stay on it or whether to give yourself a holiday in hopes that you'll resensitize the tumor. I think if that would be a very difficult study to orchestrate. I'm not sure there ever will be a study like that. So, I have no answer to that question.

*What are the practical considerations of getting a repeat biopsy?*

I think that there are many academic centers around the country that are studying this. Certainly we're studying it at Mass General. I think that, before putting yourself through a biopsy, you want to make sure there is going to be a good use for the tissue. You want to make sure you have a mechanism of getting it tested in a way that can look for resistance mechanisms. And you're hooked up with a doctor who can advise you about what you might do with the results. Basically, gear you towards the appropriate clinical trials, which may not be happening quite in the neighborhood where you live. It may mean traveling to another part of the country to be part of these trials.

I think it's kind of a cutting edge approach -- it's certainly not for everyone. It's certainly not easy or feasible for everyone. We don't know that any of these treatments work or are home-runs yet. So, it is a little bit of a gamble.

That being said, I do think that there are a handful of patients out there who have dramatically benefited from this kind of approach. And I think the more we learn about it, the more accessible it will be for everybody. So, this is the only way forward, in my mind.

**Dr. West:** Thanks. So, one question that came in is about, practically speaking, in someone who is progressed on Tarceva initially and has gotten some other treatment added to that. Say, carbo and Alimta, added to Tarceva after progression. Then they've progressed. How to do approach that? Do you reach a point where you decide that the EGFR inhibitor is not adding anything anymore? Do you continue that, or do you switch out chemos from one line to the next?

**Dr. Sequist:** Before we turn it over to any questions from people that are logged into this webinar, Dr. West had asked me to give my opinion about a couple of questions. I'll just give you my opinion, because there's no data.

I think is a data-free zone, where there hasn't been any clinical studies looking at this continuing erlotinib and switching out treatments. That is something that commonly done in breast cancer -- again, without a lot of data behind it in breast cancer. But it is extremely common practice in breast cancer clinic to continue Herceptin and switch out the chemotherapies. I have a feeling that that is the kind of direction that lung cancer is heading, data or not. So, I think you could certainly do that.

Most of the chemotherapies that we give for lung cancer are fairly tolerable when given along with Tarceva, from practical experience. I think that that would be very reasonable to do.

Sometimes, if you have a situation that you can monitor closely, you could try a holiday off of Tarceva and see if that seems to make things worse or if there's no difference. One thing about Tarceva is that it's a hard medicine to take for years on end. Your skin gets very dry; you hair gets very brittle. You have problems with your fingernails and your eyes. In some of these clinical problems, the symptoms and side effects can really be much better, even after just a short holiday from the Tarceva.

I don't think there's harm in stopping it for a short period of time in a closely monitored situation either.

**Dr. West:** Do you ever pursue a "pharmacodynamic separation" approach that has sometimes been advocated? The concept being that you don't overlap with the chemo and the EGFR inhibitor on the same exact days or two before the chemo, you'd use it a day or two later.

**Dr. Sequist:** I have picked up patients from other doctors who were already on that kind of pulsing strategy and I continued it because that's what they were doing. I do have, in particular, one patient who has been on a strategy like that for a couple of years with really good results. I also have other patients who I've just given the Tarceva. What I tend to do normally is give the Tarceva straight without any breaks. And I give the chemotherapy on whatever schedule it should be, every three weeks or something like that. So, my normal thing is not to do the pharmacodynamic separation.

**Dr. West:** What do you think about a patient who is tested and found to a EGFR wild type, but ends up getting an EGFR inhibitor and having a very good prolonged response? How do you think about approaching things when they progress?

**Dr. Sequist:** So there are a number of patients like that out there. And in the original New England Journal paper by Lynch (2004) talking about EGFR mutations, there was one patient in that cohort even who did not have an EGFR mutation, but had a dramatic and prolonged response. So, we've seen a number of patients like this. We always retest this for EGFR mutations, to find out if maybe it might have

just been missed. But I think what it tells us about the biology of that cancer is that it's dependent on EGFR signaling. It's very addicted to EGFR signaling through some other mechanism that we can't name what it is. It's not an EGFR mutation per se. But somehow the biology is acting very similar to that.

So, I would actually approach that patient very much the same as I would someone with an EGFR mutation.

**Dr. West:** Can you speak to the issue of the timeline or the arch of progression once people have developed EGFR acquired resistance? This was addressed a little bit and actually nicely, in terms of what we know right now from the Memorial Sloan Kettering publication (Oxnard, Clinical Cancer Research 2010).

**Dr. Sequist:** I think the take home point from that paper by Oxnard in Cancer Clinical Research, is that there are a number of people who can get continued benefit from staying on Tarceva if they're having a slow progression. I think why people like that Oxnard paper so much is that it kind of gave credence to what we see in the clinic. Clinicians who've treated a lot of patients with EGFR mutations will tell you that they already knew that there are two beasts. There are one with very quick progression and you have to do something else because the cancer has woken up. And there is another type of progression that is extremely slow and indolent. For those patients, you can keep them on Tarceva for many months -- sometimes even more than a year before you're really pushed to do something else.

What we do know from the Oxnard paper is that if there is no T790M, it's likely to be a bit of a faster progression than if there is T790M. But not all T790Ms are this slow progression. But if you are having slow progression and your doctor is telling you to stay on Tarceva because the progression is slow enough, that's a very reasonable thing: they're not crazy.

**Dr. West:** If someone has a biopsy at the time of acquired resistance and does have a T790M mutation, does that make you any more or less inclined to continue the EGFR inhibitor?

**Dr. Sequist:** Before the Oxnard paper, I would've have said no, no more or less inclined. I would have just based it on clinical judgment as to how they were doing. But actually, because their paper showed that there was this indolent type of T790M, it actually might make me more inclined to continue the inhibitor.

**Dr. West:** The question comes in about newer irreversible tyrosine kinase inhibitor as opposed to Iressa or Tarceva. Is there any sense that starting with one of these will extend the time until progression and postpone acquire resistance? Or do we have no data on that? What's your knowledge or understanding of irreversible versus reversible TKI's and acquired resistance timing?

**Dr. Sequist:** I don't think we have a huge amount of data on that yet. I think probably the largest study is with the BIBW 2992, afatinib. It's a study called the LUX-LUNG 2 study that is led by James Yang. It's been presented at a couple of different meetings, but it's not published yet. Not everyone in that study was first line.

Some people had prior treatment. But there a good number of patients, probably everyone in the study, had an EGFR mutation. There was a good number of people that went onto afatinib as a first line treatment. And it looks like, from what's been presented at meetings, the progression free survival, or the duration that they were on the treatment is upwards of a year. Maybe it's 14 or 15 months, which is a little bit better than what we usually see with Iressa or Tarceva. So I think there is reason to hope that these new drugs may prolong the benefit. There are a couple of studies that are ongoing with some of the other second generation drugs, that we'll see if it's a class affect or if it's specific to afatinib. But I think there is some hope to that. Unfortunately none of the second generation drugs are FDA approved yet, so you have to participate in a clinical trial to get them.

**Dr. West:** If you do continue erlotinib (Tarceva) and then add Avastin or add chemo to that, have you encountered many difficulties with either getting coverage for the new agent or continuing the Tarceva?

**Dr. Sequist:** I have not, but I go around the country and give talks to different people. I've realized that I think the insurance situation in Massachusetts must be better or more lenient than in other parts of the country. I definitely have heard stories from many of my colleagues about how difficult it can be in that situation. I think it just depends on the patient's insurance and how they operate.

**Dr. West:** Can you comment on how much or how little variability you think there might be on the location of one biopsy over another, and just cancer heterogeneity? In other words, are you concerned that whether you biopsy in one part of a cancer versus another, or in the liver metastasis versus a lung nodule that you might see very different results and be led down a very different path?

**Dr. Sequist:** That's a great question, and I think we don't fully understand the answer yet. There's been at least one autopsy case that I've seen reported where there were divergent resistance mechanisms in different parts of the patients' bodies, so one area had Met amplification, one area had T790M. So a case like that does make you worry that if you just do one biopsy, you could be misled or you can be making an assumption that's not exactly true. But I think to some extent if you're a doc or a patient who's considering one of these biopsies, you have to biopsy something that's feasible, something that's safe, and ideally you'd like to biopsy something that's growing – the site that's most likely to show the resistance mutation or resistance change.

I can say for the small cell phenomena, unfortunately one of our patients that we found this in did pass away, but did donate her body for an autopsy so that we could learn more, and in that particular patient, in every spot of cancer that we found in her cancer was all small cell and it all had EGFR mutations, so that suggested that there was some kind of master change that went on that was uniform, with the exception of a brain met that that patient had, which was still adenocarcinoma at the time of her death.

**Dr. West:** Thanks so much for taking the time to go over this with us.

**Dr. Sequist:** Sure. Thank you for having me.