



Acquired Resistance to Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors, by Dr. Lecia Sequist

Dr. West: I'm Dr. Jack West. I'm a medical oncologist in Seattle and the President and CEO of GRACE, the Global Resource for Advancing Cancer Education. I'm very happy to have Dr. Lecia Sequist here to present on a very timely topic and that is the issue of acquired resistance to oral EGFR inhibitors in the setting in advanced non-small cell lung cancer. Dr. Sequist and her colleagues in Boston have really been among the absolute leaders in the field and so she is going to speak a little on, give a summary of what is known and what are still the active questions that we are pursuing today.

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I'm going to now just turn it over to Dr. Lecia Sequist, who is Assistant Professor of Medicine in Harvard Medical School and Massachusetts General Hospital in Boston, Massachusetts.

Dr. Sequist: Thank you so much for asking me to do this. It's a real pleasure for me to talk today about strategies for managing acquired TKI resistance. And I'm sure the audience has a variety of different background knowledge about this topic, so I am going to review at the beginning: a quick overview of EGFR mutation-positive non-small cell lung cancer. This may be known information to many, but just to make sure we're on the same page to start. And then I'll talk about what we know about mechanisms of resistance to EGFR TKI inhibitors, which is another way of saying Iressa or Tarceva.

And then I'll talk about possible avenues of treating that resistance, including repeat biopsies. And at the end we can talk about some clinical, practical applications and next steps.

Just as a summary, the median survival for advanced non small cell lung cancer has improved over the last 30 years, and we definitely have a lot of room to move and improve further.

However, the more drugs that get onto the market that get approved by the FDA, the more the bar keeps moving up. At the very bottom of the screen, in these boxes, I've summarized what the paradigm of treatment has been. So, back in the 70s, if you were diagnosed with lung cancer, there really was no, many doctors would not give any treatment. They would just give best supportive care, because it wasn't thought that treatment helps. We've come a long way since then. We've gone into platinum therapies and then duvet therapies. And what people talk a lot about in the more contemporary age is targeted therapy.

And what does that really mean?

This next slide is a little bit of a spoof, but this is supposed to represent all the inner workings of a cancer cell. All of the connections and the signals and the cross talk of how the cell functions and how it multiplies and divides. When we talk about molecular targeting, or targeted therapy for cancer, what we are saying in essence is that we can understand this complicated diagram, which is reality is probably a gross oversimplification of what actually happens in a cancer cell.

But we can understand it to the extent that we can say this pathway, right here, is the key pathway and I want to block that pathway with a drug. And then we take a drug and use that to kill the cancer cells. That's what people mean when they say targeted therapy.

And something that my research is focused on is genotype-directed therapy. That just means that we can take a group of patients in the center of the screen who all have the same diagnosis: non-small cell lung cancer. Even when I was training, which wasn't that long ago, we treated all non-small cell lung cancer patients the same. There was a cookbook algorithm.

And in the era of genotype-directed therapy, we want to try and be clever enough to separate the green group of patients from the red group and the yellow group. And maybe have a different algorithm for each patient based on its genotype.

It's recognized that not all non-small cell lung cancers are the same.

And another analogy that I like to use is that, in order really get to the gold in the safety deposit box, there's really two key steps. One, you need to be able to open the vault. But two, you need to have the key to the individual box that you've got there. So this represents what I think is our challenge in cancer therapy is that we not only have to understand the very complicated biology and the inner workings like that complicated map, the wiring of the cell. We have to be able to understand the biology of the cell. So that's getting into the vault. But we also have to have a very important piece, which is the key to our own safety deposit box. And that's the analogy that I think of as the drug.

In some cases, we have the drug that seems to work. But we don't really understand the biology of the cancer well enough to know how to use it. In other cases, we understand the biology of the cancer, but we don't have the right drug that's specific enough or safe enough to give. So, really the sweet spot is when you understand the biology and you have the drug that's tolerable and effective. Then you can get to the gold or the pearls or whatever you've got inside.

So, what we're talking about today is EGFR mutations. This is a CT scan, a chest CT scan with an EGFR mutation who had a lot of cancer in the right lung. You can see before, he's bound to have an EGFR mutation. He was treated with a personalized therapy, something like Iressa or Tarceva. And just a few weeks later, you can see a very dramatic response. That's what we're hoping for and that's the goal for all lung cancer patients. It's to understand the situation enough and to have the drugs to get to that type of response.

How does an EGFR mutation cancer differ from any other type of lung cancer? This diagram is trying to depict the signaling in the cell. Every cancer cell has to receive signals that tell it to grow and multiply and divide. The difference between an EGFR mutation-positive lung cancer, which is listed here as gefitinib-sensitive -- gefitinib is just another name for Iressa -- the difference between that and another cancer cell is that all these pathways are very reliant on EGFR.

EGFR is like an antenna on the surface of the cancer cell and it sends out a broadcast. These cancer cells, that's their favorite radio station. They don't like to listen to anything else because they are so addicted to that radio station, if you shut it down with a drug like Iressa or Tarceva, you turn off the radio station, then the cells die because they don't have their signal. And this differs from a more typical cancer, lung cancer, that has lots of different antennas or radio stations on its surface and broadcasts lots of different messages.

So if you were to block one of them, the cell can still live and persist because it gets signals from other places. So that's the dilemma here. This past year or two has been very exciting because we finally have randomized trials that support what many lung cancer researchers have thought for several years, which is that, giving patients with EGFR mutations drugs like Iressa or Tarceva can really make a difference.

Many of you might be familiar with the IPASS trial, which was published a year and a half ago now in the New England Journal of Medicine. This was a landmark trial done in Asia. It wasn't specific for patients with EGFR mutations, but they had a very good clinical selection by doing it in Asian countries where the frequency of the mutations is about two or three fold that in the western part of the world. They used patients that were all, never smokers. Ninety-six percent of the patients were never smokers. They were randomly assigned to receive Iressa, or gefitinib, an EGFR blocker or chemotherapy with carboplatin and paclitaxel.

They looked at how patients did and, if you're not familiar with looking at these types of curves, this is a Kaplan-Meier curve. And we use it to show how well people do on a treatment, the higher the curve stays up towards the top, the better. The faster it drops down towards the bottom of the graph, the worse. The yellow line represents the patients that got chemotherapy. The green is the patients that got Iressa. They cross, which is somewhat unusual to see, especially in a clinical trial that is positive, as this one turned out to be. Essentially, without getting into too much statistics, the reason why these lines cross is because they are two very different populations comprised within the study. There's patients with EGFR mutations, and patients who were negative for EGFR mutation.

And when you look at them separately, the lines don't cross. What you see, for those who had an EGFR mutation, the green line, or the Iressa, stays up higher longer. And the chemo line drops quicker. This was a very big advance, and I think really changed the mind of a lot of oncologists who were skeptical about this phenomenon of genotype-directed therapy. What the slide is looking at is the progression through survival. Meaning, how long can you stay on the drug before progressing? What I think actually has made the biggest impact in the

United States as far as practice in the community is this half of the slide, the right slide. Looking at the patients that are EGFR mutation negative. As many of you probably know, testing for EGFR mutations is a bit complicated. You need to have enough tissue, you need to have a lab that will do. You need to have someone who will pay for the testing.

Many people thought, we have some clinical predictors, we know that women or patients with adenocarcinoma or never-smoking patients are more likely to have these mutations. Why don't we just use that as the surrogate and treat those people with Iressa or Tarceva? And this right hand side of the curve is what really, I think, changed practice. What this shows -- remember everyone in this trial had adenocarcinoma and was a never-smoker -- but if they didn't have that genotype, if they didn't have an EGFR mutation, they actually didn't do very well at all with Iressa, and chemotherapy was much better.

So I think this helps to convince oncologists. Whether or not you have the mutation, you want to give your patient in front of you the best possible treatment for them. Personalized medicine is really appealing for the patient, it's appealing for the doctor. It's a win-win situation. I think that this trial had a lot to do with bringing personalized medicine into the everyday practice of lung cancer.

But what we're really here to talk about today is resistance to these treatments. This little cartoon shows the summary of what we know so far about what know about resistance to drugs like Iressa or Tarceva. We already talked about the paradigm here. We have a sensitive cell and you give a drug/a TKI like Iressa or Tarceva, and you shut down all of these downstream pathways and you get tumor cell death, which is the goal.

There's two main mechanisms to resistance that we know of that are very commonly found. One is a second type of mutation in EGFR called T790M. What that does is, it changes the interaction between the EGFR antenna and the drug. So the drug can no longer get in and block the signal the way it could before. The signal turns back on. The downstream pathways turn back on and the cancer cell is happy. This is the most common mechanism of resistance.

Also, MET amplification has been another established mechanism of resistance that happens in lung cancer models in the laboratory and also has been shown to occur in patients -- a smaller percentage of patients.

The situation here is that the cancer cell is not getting the signal that it craves, that it is addicted to from EGFR, so it throws up some other antennas. It puts up lots and lot of MET, which is another type of signaling receptor. It can generate similar signals. So, it may not be exactly the same as EGFR, but it's close, and the cell is happy and can survive even though it's close enough to EGFR. So these are the mechanisms or resistance that have been well described so far.

What I'm going to talk about in the next couple of slides is how well are we doing on what I think is the new paradigm? Or how far do we have to go to get to this new paradigm? We've talked a little bit about getting an understanding, a biopsy, to look at both the type of cancer that you have, but more importantly the genotype, some of the molecular information at the time of diagnosis, so that you

can give a targeted, or personalized, therapy to a patient, which is maybe a pill. Many of the newer treatments are pills. But the reason why this is a circular diagram is that this is not enough.

After that first targeted therapy stops working, we have to go through the whole circle again. We have to take a look at the clinical information. But I think it's very important to try and get a biopsy and figure out, molecularly, what's going on now. That's the only way we're going to be able to move forward and figure out what the next type of targeted therapy is going to be for that type of a patient. So, let's talk in a little bit more detail about these two mechanisms of resistance to Tarceva or Iressa.

So T790M, this is that mutation in EGFR, it was initially reported to happen in about 50% of patients. But there has been a number of studies that show it to be higher, up to 70 % of patients who become resistant to these drugs. Our colleagues at Memorial Sloan Kettering published an interesting paper just a few months ago showing that the prognosis of T790M may be slightly better than other types of resistance to Tarceva. This is another type of marker. The line on top is showing patients that had T790M demonstrated when they became resistant compared to people who were tested and were negative for T790M. As far as how to treat this kind of resistance, there was initially a lot of enthusiasm.

This is a relatively old paper from a group here at my hospital looking at a drug called HKI-272, which was made by Wyeth. It's a similar type of drug to Iressa; it's an EGFR inhibitor. It's irreversible, and the thought was, from the laboratory work is that, if you had a irreversible inhibitor, it could get around T790M. These lab results basically show that, in a petri dish, this worked. You could demonstrate that a cancer would have T790M, but it would be killed off by this drug, HKI-272. So, we tried this in patients and, unfortunately, the results in patients weren't quite in spectacular as they were in the petri dish. This was the study that was just published last year in the Journal of Clinical Oncology. It looked at this drug, HKI-272, in patients with a particular, this column here, arm A, we had 88 patients who had an EGFR mutation, had already been treated with something like Iressa or Tarceva, but then became resistant. They were put on this drug, and only 3 % of the patients responded. So that was a little bit disappointing. So, this is a graph showing the people that responded. Everyone starts off at baseline with their tumor. If their tumor grows, that's depicted here over on the left hand side of the curve.

If the tumor shrinks, it's depicted over here. So some people have some shrinkage, mild amount of shrinkage. People had mild amount of growth. There were a couple of people, over here, who had dramatic shrinkage to this drug and that was very interesting. They all had a specific type of EGFR mutation called deletion (exon) 19. So that's a little bit off the topic of today, but this drug may be particularly effective in patients with a deletion 19 EGFR mutation.

See here, that all these little bars where there's a "T" that represents a patient where we knew, through a biopsy, that they had T790M. As you can see, some of those patients responded a little bit. Some of them -- most of them -- did not respond. But there were no dramatic responses in patients with T790M, with this drug that was hoped to be very helpful for T790 M.

There are other drugs which are similar to HKI-272 that have been, I would say, equally disappointing in this situation. There was a drug made by Exelixis which had a 2 % response rate in patients who were resistant to Tarceva or Iressa. The Boehringer-Ingelheim drug which has a name of afatinib also had a very low response rate of 7 %. I'll talk a little bit later about an interesting ongoing study combining afatinib with cetuximab, which is an IV treatment that's an EGFR blocker, but it's an antibody. So, there may be some success in blocker EGFR through two different mechanisms. Pfizer also has an irreversibly EGFR inhibitor. Here again, the response rate was only 7%. So, we initially thought that this class of drugs would be a home run against resistance. Unfortunately, we were wrong in that regard.

But remember what I said in the beginning: that you need to understand the biology, which in this case, I think we have the biology. History might prove that it's more complicated. But we don't have the drug. We don't have the key to the lockbox here. So, what we need is a better drug. There is hope. There is a new class of drugs that are EGFR inhibitors that are coming forward that are potentially supposed to be more effective against T790M.

This is a structural model of one of these drugs, which currently is called WZ4002. It doesn't have a better name yet. This drug is not even to the point where it's in human trials. It's still in pre-clinical trial, testing it in animals. So, there are some other drugs that are similar to the WZ compound that are also in pre-clinical development. So, we'll see. I have high hopes for this category of drugs. But we're a long way from knowing the answer.

So, we'll come back to T790M in a few minutes. Let's switch gears for a second to MET amplification. Again, these are some basic kind of slides that just describe MET amplification was discovered by my colleague, Jeff Engelman.

I think that this cartoon is a bit easier to understand. Basically, we've talked about this before, where you have this EGFR addicted cell line and it's sensitive because of an EGFR cell mutation. One of the key signaling pathways in any EGFR addicted cancer is through ERBB3 or Her-3, it's also called. ERBB3 or Her-3. This goes down through the PI-3 kinase and AKT pathway. When you give Iressa this whole pathway down and when you become resistant through MET amplification. Basically what MET is doing is it's giving a secondary signal to ERBB3, so that turns on that downstream pathway. The cell is happy.

The difference between this and T790M is that in order to now kill a cancer cell that looks like this, you have to still block EGFR and well as blocking MET. You can't just switch to a new drug. You have to add something in. So I think, effective strategy to treat MET amplification as a resistance mechanism will involve at least two drugs: one that hits EGFR and one that hits MET.

To give you an anecdotal example of a patient of mine, this is a 63-year-old gentleman with an EGFR mutation who, here's what his tumor looked like in his right lung in the beginning, right at the time of his diagnosis. He was treated with Tarceva and had a very dramatic response. But after about a year, which is an average amount of time to be on Tarceva, he developed resistance.

This picture here shows a needle going right into his resistant cancer, where we did a biopsy to try and figure out why he was resistant. What we found on that biopsy, was indeed, that he had MET amplification.

So this is a FISH (fluorescence in situ hybridization), a certain way of looking at cells to see the genes inside. This is his baseline FISH back in 2008 that showed normal copies of MET. Each red probe had a matching green probe and they were nicely paired.

But in 2009, when he was resistant, there was many, many more red signals compared to green signals. So this shows us that MET was amplified. This patient was actually treated on a clinical trial. Because of this finding, we put him on a clinical trial of an EGFR blocker, plus MET blocker and he had another response, which lasted for a good long while on clinical trial.

This is just one anecdotal example. But he's one of a few patients that have convinced me about the benefit, the potential benefit of doing these repeat biopsies. We can all understand the benefit, or the research community, the benefit as far as gaining further knowledge of doing these repeat biopsies. But I think it's more than that. I think there's actually benefit that could come to patients, if we can understand their personal mechanism of resistance and we can then strategize about the most effective treatment to try for them. And there are many clinical trial available around the country as we'll talk about in a few slides.

So, just to summarize where we're at with MET inhibitors: MET inhibitors are relatively newer onto the scene that some of the second generation EGFR inhibitors. A couple of the main drugs are listed here on this slide, but I don't think we have yet a real definitive study that's looking at the question of interest to this group. There is drug by Arqule and Daiichi-Sankyo: ARQ-197. The trial was done looking at erlotinib and that drug. But it wasn't in the acquired resistance setting. It wasn't in patients who had an EGFR mutation specifically. So those results were presented by Joan Schiller at ASCO last year. We'll hopefully be coming out in press soon, but I don't think that's entirely applicable to this situation.

And the same with the imatinib drug. This is a monoclonal antibody which targets MET, but again, the first big study that's been presented now by David Spiegel looking at this drug wasn't really designed for the question of acquired resistance among EGFR mutation positive patients. There's a MET inhibitor by Exelixis, called XL-184. Results of that trial have not yet been reported. Then, our old favorite drug, which you may not know by this number, PF-02341066. This is crizotinib, a drug that's been in the news a lot because of its ability to help patients without translocations. It's a very exciting story for another day, in lung cancer. But crizotinib was initially developed as a MET inhibitor. There are on-going studies looking at crizotinib looking at patients with EGFR mutations, who may have developed resistance to Tarceva due to a MET amplification.

So, I know some of this news that I just went over, the results are a little bit discouraging because so far we don't have a home run as far as EGFR

resistance. But there are many on-going trials looking at novel ways at attacking resistance. I've listed just a few here. There's the multi-site trial going on through the Lung Cancer Mutation Consortium with the drug called MM-121, which is a HER-3 monoclonal antibody along with erlotinib. I mentioned before briefly that there's a trial with afatinib, that's BIBW-2992 along with cetuximab, which is being led by Vanderbilt University and Memorial Sloan-Kettering.

There's this crizotinib-based study, using the Pfizer EGFR inhibitor along with that. Then there are other classes of drugs that are being investigated. This list is, I'm sure, not comprehensive. This is just meant to be a representation of what some of the studies are that are going on. Different groups are looking at HSP-90 inhibitors, HDAC inhibitors, PI3-kinase inhibitors, and the list goes on and on. So there's definitely a lot of enthusiasm about trying to find the best treatment for EGFR resistance.

So what about repeat biopsies? If you're thinking about this with your doctor, or you know a patient who's thinking about this with their doctor, the pros are that you may be able to be altruistic and help the field discover more about resistance to these agents. But I think that for an individual patient who's considering a biopsy, the big selling point is that we may be able to uncover information specific to that patient, that would help gear them towards the most appropriate clinical trial that might have the best chance of working.

Of course the cons, or the downsides of doing the biopsy, are the cost and the safety. I think that the cost certainly varies depending on what type of biopsy you do and who does it and what's the insurance situation. It's hard to put a number on the cost. Safety, in the reported series, it's actually pretty good so far. There's a couple of groups who have talked about the safety of doing biopsies in patients who already have a diagnosis. In other words, you're not getting the biopsy to find out what kind of cancer they have, you're getting it for some other reason. MD Anderson has presented their paper at meetings and it will very soon be coming out in press about their BATTLE study, where they were biopsying patients to look at different bio-markers and they had a very good safety record with that. Memorial Sloan-Kettering has published their experience specifically in EGFR mutation positive patients, looking at the safety of repeat biopsies. That's in Clinical Cancer Research last year. Again, they had a very good safety record.

Mass General will be publishing our experience in about two weeks looking at repeat biopsies. We also didn't have any complications really. In general, these biopsies are fairly safe. But that doesn't mean that there aren't other downsides to going through biopsy. It can be painful. It can be inconvenient. There are many groups working on other alternatives to biopsy that are less invasive. They're looking at things like circulating tumor cells or different serum markers. There's certainly a lot on the horizon as far as improving that.

Are there any other things that we can do to learn about acquired resistance or treat acquired resistance differently?

There's a lot of discussion if you go to meetings and talk to lung cancer doctors. Everyone hopes to do combination therapies just because medicine has had a lot of success in treating other diseases like tuberculosis or HIV or even lymphoma,

another type of cancer, with combination drugs. And hitting a cancer from multiple aspects at once sure does seem appealing intuitively. Logistically this can be somewhat difficult to study. Many of these drugs have overlapping side effect, especially the newer, targeted drugs that target a specific gene or mutation have overlapping side effect. This can mean combining them is difficult.

Then there are all these other political and business-like type of red tape lines which are that many of these drugs are made by different companies. Companies aren't always willing to work together with another company before their drug is FDA approved for fear that could be a lot of toxicity that could end up killing their drug in the end. So there are a lot of real-world hurdles to that strategy.

We've been looking at whether or not you can identify how cancer will become resistant before you start on therapy so that maybe you can give a combination therapy to begin with that would be more specific for that patient. Then of course, are there other therapies or strategies that you could try? Just thinking about identifying the eventual mechanism of resistance for a given patient, in leukemia there's some data to suggest that these resistance mutations exist even before you even start treatment. We have seen this a little bit when we looked at EGFR mutation positive patients with an ultra-sensitive assay called the DXS assay. We saw that many patients had detectable minute levels of T790M even before they even received Iressa or Tarceva. In general, those patients who we could detect T790M, had a shorter duration that they were able to be on the drug because they developed resistance more quickly. So that's for T790M.

Jeff Engelman's lab has shown that you can also detect vary low level of MET amplification in cell lines in this case that were treated with an inhibitor. I think this is an area of research that's going to be moving very quickly forward in the future. Can we preselect which patients might develop which type of resistance and try and nip it in the bud, so to speak.

So, in some way, the research focus, I think, is genotype-directed therapy is off to a really good start. There's been a huge advancement in this area over the past five years, but there is significant room for improvement. There are a lot more questions that we have to tackle and treatment of resistance is the biggest one. It's proven to be more complicated than initially hoped, but many trials are on-going.

Many patients are benefitting from these trials. I think that prevention may be a potent strategy, especially because previous decision toward certain mechanism of resistance look like they can be identified and this I mentioned we need less-invasive alternatives to these biopsies.