



## Lessons Learned from Serial Biopsies of Patients over the Course of Treatment with Acquired Resistance to Oral EGFR Inhibitors, by Dr. Lecia Sequist

**Dr. West:** Hi. I'm Jack West, Medical Oncologist, and the President and CEO of GRACE, the Global Resource for Advancing Cancer Education. I'm happy to have Dr. Lecia Sequist from Mass General Hospital Cancer Center and Harvard Medical School. She's an Assistant Professor of Medicine there, and she is here today to provide additional information that was not able to be included in the initial podcast because it was about to be published and it has since been, so it is now available for the public and she can tell us about the truly most recent information about re-biopsies in the setting of acquired resistance and what that might tell us.

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And with that, I will turn it over to Dr. Sequist.

**Dr. Sequist:** Okay. As we were talking about in the previously-recorded podcast, I think an important strategy going forward with learning about patients with oncogene-addicted tumors and how best to serve them with treatment is this concept of going around and around this circle of trying a targeted therapy after gathering clinical information such as the treatment worked or the treatment didn't work, then thinking about reanalyzing the tumor and seeing how it has adapted or evolved in response to that therapy with a repeat biopsy or potentially future technologies that are less invasive.

And I'm happy to be able to tell you a little bit about this paper that we recently published, and I have to definitely acknowledge all of my co-investigators as listed here. It was a group effort by a lot of smart people to try and get this group of patient data together.

Essentially what we did is we looked at 37 patients, all of whom had EGFR mutations and had responded well to their treatment first time around with either Iressa or Tarceva, but then after a period of time had acquired resistance to the drug and had undergone a biopsy in that drug resistance state. And I think the really interesting thing about this study is that we were able to compare pre-treatment and post-treatment tissue on all of the patients, and that's why we had a smaller number, because we did have a larger number of patients who were biopsied, but we only included the people who were able to be compared and really document for sure what the changes were.

Now this pie chart is a grand summary of everything that we've found, and so I'll go over it in a little bit of detail. But I think the bottom line is that we saw some of the things we would expect to see that had been published before, and we also saw a couple of new findings that were a surprise.

And so the blue here, which takes up about half of the pie, is T790M, which we spoke about before. This is a second mutation in EGFR, and one kind of interesting thing is that we saw a subgroup here of the T790M patients also had acquired amplification of EGFR, meaning there were lots and lots of extra copies of EGFR bearing that T790M mutation, so it was something a little bit novel, and something for the scientists to continue to work on to understand exactly how that might contribute to the development of resistance.

We also saw in this green wedge of the pie amplification of the c-Met gene, which we had talked about as being one of the previously described mechanisms. And then some of the new unexpected findings we had were that we had a couple of patients here in yellow with a PIK3CA mutation, this yellow wedge, and actually this orange wedge both represent patients that had this mutation. PIK3CA is another signaling receptor in a cancer cell, and its downstream of EGFR, and also of Met, and also of a lot of other key signaling pathways. And the reason why that was exciting or important is that there are actually a lot of drugs coming out against the PIK kinase receptor that may be active in patients with this PIK3CA mutation, so that's something you can potentially act upon if you have that mutation found.

And the most surprising finding, I think, of the study was that there were five patients here, the red and orange combined wedges, that had undergone a major transformation that is just kind of a little outside of how we normally think about lung cancers behaving. They had gone from having adenocarcinoma at baseline, which is a type of non-small cell lung cancer, to their resistance biopsies showing a total transformation to a different type of lung cancer called small cell lung cancer. And one of these patients had both the small cell and the PIK3CA mutation, so that's what the orange wedge means – a combination of the yellow and the red.

So just a little bit more information about this small cell lung cancer transformation: These are pictures of what cancers look like under the microscope when pathologists look at them, and the pre-treatment row here on the top shows what an adenocarcinoma usually looks like. And this resistant biopsy shows what a small cell carcinoma usually looks like -- the viewers don't have to be completely versed in all of this, but you can see from across the room that these cancers look very different and stain differently with some of these chemicals that we put on them. And this was surprising for everyone. This was just not the behavior that we expected. It's normally conceived of that non-small cell and small cell are completely different kinds of cancers, and small cell would be very unlikely to have an EGFR mutation. And in fact, all five of these patients when they had small cell, they maintained their original EGFR mutations, so these cancers were clearly *derived* from the prior adenocarcinoma.

And then this x-ray (*sic*) is just to point out or to illustrate that these patients that were found to have small cell lung cancer, some of them were treated with a traditional small cell lung cancer kind of chemotherapy, a platinum/etoposide chemotherapy, which is not typically given to adenocarcinoma. It can be in some situations, but for the most part this is the type of chemotherapy that their oncologists weren't necessarily entertaining giving them. And here, for example: this is a chest wall mass of one of these women that we biopsied. This was a very

painful tumor growing around the rib, and after just a few weeks on the chemotherapy aimed at small cell, it really shrunk down to almost unmeasurable – this is just her normal rib now. And the same goes for a lymph node that was in her armpit over here and was quite big. You can see it's kind of bulging out her skin, then it shrunk down to the normal size of a lymph node. These cancers can be very sensitive to chemotherapy that you might not have otherwise thought of giving your patient if you hadn't done the biopsies, so I think this really impacted patient care as well as being very interesting scientifically.

And then the final finding from our paper that I really wanted to highlight is depicted on this cartoon that shows that some of these resistance mechanisms can wax and wane over time. This pattern as depicted on the top was seen on a couple of different patients, so this is just one representative patient. But you can see that the patient started off with adenocarcinoma, and an EGFR mutation, specifically the L858R mutation. And when they received, this up and down little bar here is just a gross depiction of whether their tumor was growing or shrinking; it's not quantitative. But their tumors shrunk when they were getting Tarceva, and they became resistant and had a biopsy with us showing that they had acquired this T790M resistance mutation. And so then over the next year and a half, this patient was off Tarceva getting a variety of different chemotherapies, and then had another biopsy right before starting a second course of Tarceva, and the T790M had disappeared.

In other words, after a year and a half or so of being away from Tarceva, which was apparently exerting some kind of selective pressure on the tumor to make the resistance mutation come out, that resistance mutation went away and this patient actually had a second response to Tarceva. Now this is something that we've seen described in many, many patients that after a break from treatment: sometimes they can re-respond. But this is one of the first times that anyone had ever documented this resistance mutation actually comes up and then goes away, and that that may be a way that you can test and tell whether someone is ready to re-respond to treatment.

And then a similar type of concept here on the bottom: This patient started off with adenocarcinoma and an L858R mutation, was sensitive to the Tarceva for a long time. At the time of resistance, underwent a biopsy; and this is one of our patients that actually transformed to small cell lung cancer. And so the Tarceva – she still had the EGFR mutation and also this other PIK3CA mutation, but Tarceva was halted, and therapy was switched over to a small cell type of treatment. And after a while, it was about ten or eleven months in this patient, she underwent a second biopsy – again, a second repeat biopsy, and now the tumor had basically transformed back to adenocarcinoma, and also this other resistance mutation PIK3CA had disappeared. And so she, too, had a repeat trial with Tarceva and had another response, although this one was shorter-lived -- about six months in duration. And then a repeat biopsy again when she became resistant the second time showed that the cancer had transformed back to small cell. So this is a very fascinating case study of a small group of patients who underwent serial biopsies over the course of their treatment, and we saw that the resistance mechanisms waxed and waned.

So I think in summary, what we have learned from this study is that acquired resistance to EGFR TKIs is indeed a very complicated phenomenon that requires more study, and the more we learn, the more we want to know. And it's just like we're opening Pandora's box here, but I think for patients and for oncologists, one of the most important lessons to me is that repeat biopsies and sometimes multiple repeat biopsies over the course of time can be informative and can help patients in real life decisions. It may help choose a clinical trial that makes the most sense for a patient, and it may help you understand if a repeat trial of Tarceva is likely to work.