



## **2020 Target Therapy Forum**

### **EGFR Session**

# **Current & Emerging Treatment Options Upon Acquired Resistance to Osimertinib- Part 2**

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Dr. Zofia Piotrowska: So how does osimertinib resistance develop? And, you know, this is kind of a schematic, which I think helps put these different resistance mechanisms that we've learned about into kind of a framework. And this is a framework that we also use with older types of EGFR inhibitors. And indeed is a framework that in the ALK session right now, they're also using to talk about kind of how cancers can become resistant to targeted therapies. But generally, you know, if you think about the EGFR kind of pathway where this is the EGFRs protein that sits on the surface of the cell and it activates these downstream pathways, resistance can, you know, cancers can become resistant by a few different ways. So one is by actually altering the target the EGFR itself. And in that situation you know, that what we're looking at for osimertinib resistance is a C797S mutations, which you might've heard of heard about, or some other more rare EGFR mutations like G724S and others. Cancers can also amplify EGFR where they put up more of these EGFR proteins on their surface to try to overcome osimertinib.

And with the older drugs, T790M, which was another acquired secondary EGFR mutation also worked through this pathway. In the past, that was the kind of the most common resistance mechanism that we saw in patients who had progressed on erlotinib and gefitinib. But what I'll show you over the next few slides is that this is no longer kind of the main dominant driver of resistance and that the pattern of resistance has become a lot more complicated with smaller kind of pieces of the pie of resistance mechanisms seen in different patients. We also see this broad category that's called bypass pathway activation, or basically cancer cells, rather than relying on EGFR, which is being



effectively suppressed by those osimertinib might say, okay, well then I'm going to upregulate these other pathways that work in parallel to try to activate the cell and allow it to start to grow and divide again, the most common one of these that we see as MET amplification.

So MET is a parallel signaling pathway, which can also be upregulated amplified, where you have more of these copies on the cell surface. And that allows that cell to start to grow and divide again. And as I'll show you in a few slides, this is something that we can potentially target by if we can block EGFR and MET together for patients where MET seems to be driving resistance. In rare cases, we've also seen activation of other pathways, including BRAF, RET, ALK and other fusions that emerge after resistance to osimertinib. And we've also seen as a, I already alluded to kind of things that don't neatly fit into this picture here, which are the histologic changes where the cancer actually interchanges fundamental properties about the histology of the tumor to grow despite the osimertinib and the most kind of well-described of those is the cell transformation. But as I alluded to others, including squamous cell transformation have been identified, and I'll stop here to say that really, you know, this is by no means an exhaustive list.

I think what we know now is that probably cancers are figuring out ways around osimertinib through other pathways that we haven't yet been able to identify and a lot more work needs to be done to try to get it, not just these genetic changes, but other ways that cancers may [inaudible] to become resistant to targeted therapy. But these are the most common ones we've seen so far. So this we already alluded to these are really not meant to be to scale, but just to kind of highlight the fact that and for patients who are treated with erlotinib and gefitinib, the older drugs, for years we were in a situation where about 50 to 60% of patients developed the secondary mutation T790M, when they progressed. And for those patients osimertinib was actually a highly effective therapy. Osimertinib, as Jared nicely outlined was then move to being a first-line therapy, an initial therapy for patients. And what we've seen so far with osimertinib resistance is that this pie has become a lot more complex. Resistance has become more heterogeneous.

And it's not that if we come up with one therapy, we're going to be able to kind of catch a large percentage of patients who progress on osimertinib. We're probably going to have to develop multiple different strategies to address all of these different pathways. What do we know specifically about resistance to first-line of osimertinib? Osimertinib used an initial therapy? The truth is that we still, the knowledge that we have is still relatively limited and I've shown really the two largest data sets that we have so far of patients who have progressed on first-line osimertinib. And I'll highlight here that in this study, there was 91 patients included and here at 27, so still quite small numbers. This



was the result of liquid biopsies circulating tumor DNA analysis done from patients who had progressed on osimertinib within the FLAURA trial. And here, what we can see is that among these patients, about 7% of them progressed through this EGFR C797S mutation. And about 15% of them had MET amplification. Importantly, this was a CT DNA based test. So we could not find how many of these patients had had histologic changes.

But in the Memorial experience, which has shown here 27 patients were included, but these were tissue biopsies obtained from patients who had progressed on first-line of osimertinib. And here, what was surprising to see was that in total, about 15% of the small cohort had histologic transformations. So we had Trent patients who developed small cell or squamous cell, as well Pleomorphic carcinoma, which is a more kind of mixed appearing tumor. And what we can see here is that, you know, on this pie chart, transformation does seem to be a larger piece of the pie than we might've expected based on older studies where small cell transformation accounted for probably about 5% or so of patients who progressed on erlotinib and gefitinib. I will say that I think we need to remember here that the caveat to this data is that is a relatively small data set. We're only looking at 27 patients. We're also looking at patients who are probably the first to progress on osimertinib since the time it became widely approved and available in this country. And so I think that this pattern, this pie chart may change with longer follow-up, but nevertheless, I think transformation is something that has to be identified, and looked for.

In this cohort, 7% of the patients had MET amplification, and we did see a handful, probably just a single patient with acquired fusions and some of these other bypass genes that I mentioned, like RET and BRAF and others. So how do we think about treating these patients? You know, once we've assessed the resistance mechanisms, we're thinking about a switch in systemic therapy, what do we need to be thinking about? And I wanted to just spend a moment kind of talking about some of the treatment options for patients with these various types of resistance. Although I will say that, you know, we have to recognize that really for the majority of patients who progress on osimertinib today they will not have one of these identifiable resistance or targetable rather resistance mechanisms that was seen on biopsy. So, I think it's still important to do these biopsies, because if we do find one of these resistance mechanisms, it can open up treatment options, which may we may not otherwise know are right for the patient, but it's also, you know, I think as a patient going into a biopsy, you know, realistically the likelihood is that there won't be a resistance mechanism.

And then we'll be thinking about broader types of treatment like chemotherapy, which can also be a very, very good approach. And I'll touch on that at the end for patients. And again, it looks like about seven to 15% of patients perhaps progressing on



osimertinib from the limited data we have so far, who developed amplification after frontline osimertinib, we do know and have good data to suggest that using a combination of an EGFR and MEK targeted therapy together can work after osimertinib alone is no longer effective. And the data here is, you know, the largest data set that was just recently published is from something called the Taton study, which looked at the combination of osimertinib with the MET inhibitor, savolitinib. And here, there was a cohort of patients who had progressed on a prior third generation EGFR inhibitor, like osimertinib or other experimental drugs in this class. And they showed that there was about 30% of these patients crossed that, that threshold of 30% to have a partial response.

Although, again, if you look at this waterfall plot, like Jared explained earlier, if you look at each of these bars as an individual patient, you can see that many had tumor regressions as a result of the combination. Then we think this is an active type of treatment, and there are several trials I'm going now testing this combination. For patients who can not go onto a clinical trial, who may not have access to these trials where they are, may not be able to travel for them. There is also some data primarily from case reports, looking at the combination of osimertinib with a drug called crizotinib or its brand name is DelCory, which is a drug that is often being talked about in the ALK session right now, it's actually a drug that's FDA approved for ALK and ROS1 positive cancers, but was originally developed as a MET inhibitor. And we've seen that the combination of osimertinib with crizotinib can also yield regressions in tumors. And I've shown you a picture from a case report that was published a few years ago here, looking at lung cancer that shrank with the addition of crizotinib after MET amplification was identified.

So, we do sometimes think about this for off-label use since both of these drugs are FDA approved. If patients have met amplification and we don't have access to a clinical trial. For patients with EGFRs C797S, which is this tertiary mutation in EGFR that blocks binding of a osimertinib, and causes develop the development of acquired resistance, the treatment strategies, there are some emerging treatment strategies. Although I will say that these are also still quite experimental and we're still learning quite a bit about them. So over the past couple of years, we have seen that in early studies of some of the drugs. In fact, some that Jared already mentioned Amivantanab , or J&J 372, which is a by specific monoclonal antibody that targets both MET and EGFR. In this original study. There were a few patients with C797S who had responses. Similarly, a drug called very creatively named U3 1402, which is what's called an antibody drug conjugate targeting a molecule called HER3 in the EGFR pathway that drug also in early phase, one studies showed a few responses among patients with C797SS.



Now with these drugs, I think it's important to remember that we're talking about a handful of patients in each of these cases, really less than 10 patients who responded. And so this is exciting to see, but we need a lot more data to really be able to know which of these drugs are the right ones for C797S patients. There's also been some thought that perhaps first-generation EGFR inhibitors, which don't form a covalent bond at C797S the way that osimertinib does may still work for patients who develop C797S. And there have been some case reports of using that. And again, because first-generation EGFR inhibitors like gefitinib and erlotinib are available, we do sometimes reach for this in an off-label fashion. But I think that it's, it's still something that we need to learn a lot more about. And then finally, the combination of osimertinib with the anti EGFR antibody, necitumumab has also been tested, and a handful of patients have responded. So, you know, what do I take from this?

If you have, if you're a patient or the loved one of someone who was found to have C797S, I think it is important to talk to your doctor about referral for clinical trials, but outside of a clinical trial right now, I think chemotherapy, as I alluded to as an effective treatment strategy for these patients, and is my preferred approach for C797S at this time. And I think, you know, if you don't have access to a clinical trial chemotherapy can work very well for these cancers. I wanted to spend a moment talking about small cell transformation, which I already kind of introduced, because I know there has been a lot of concern and appropriate worry about this from patient groups and patient advocacy. And in particular, this question of, you know, our transformation is more common and when patients receive first-line osimertinib, and is that something we should be concerned about? Histologic transformations to small cell carcinoma have really been seen to occur after all classes of EGFR inhibitors. And while I think there's been a lot of talk about small cell transformation in recent years, particularly because some of that early data with first line osimertinib did show that histologic transformations numerically maybe a little bit more common.

I think it really, we have to be careful to assume that they're going to be more common with osimertinib than with older classes of drugs. Because again, we just don't have enough numbers or follow up to really be able to say anything like that with confidence. Nevertheless, I think histologic transformations are important and, you know, are a very important to look for. We do know that there are some risk factors, including the co-occurrence of certain mutations and in particular mutations, EGFR TP53 and RV1, when patients have all three of those together at the time of their diagnosis on their next generation sequencing report, we know that those patients are at increased risk of having a small cell transformation down the line, but yet not all patients with those mutations will eventually undergo a transformation. And I think this can be a great source of anxiety and worry for patients understandably today. Unfortunately, I wish I



could tell you that we had a plan of how we could address that upfront and then be able to say, okay, you have this risk factor. Here's how we're going to follow.

Or you know, here's an intervention that we can do to decrease the risk of transformation. And we don't have that yet. Although we are working to try to develop those types of strategies. You know, I think at present for patients who have those mutations, I watch them closely. And I certainly think about a biopsy when they do progress. And I think, you know, but I don't change my kind of treatment practice based on these mutations right now, as I alluded to small cell transformations at present can only be identified by tissue biopsy. But when we do identify them, they can respond very well to small cell directed chemotherapy. So typically we use platinum and etoposide chemotherapy, like we do for other small cell lung cancers that didn't arise from EGFR mutant cancer, and those can be very effective. So this is something that that is important to be aware of and for both patients and providers, to be aware of. Finally, in the last few minutes, what about chemotherapy?

As again, I already alluded to, I think we talk a lot about resistance mechanisms to osimertinib, but today in my practice, I still, the majority of patients don't have a targetable resistance mechanism that we can identify after osimertinib. We hope that will change with time as we develop a better understanding of osimertinib resistance and also better targeted therapies for different types of resistance. But today for many of my patients, you know, if they don't have, for example, MET amplification, I didn't touch on here because they're quite rare, but also just to mention patients who do have acquired fusions in a RET or an ALK, or BRAF, these are, you know, only occur in a few percent of patients who progress on osimertinib, but if we do find them using combinations of, for example, a Rex targeted therapy and osimertinib can be effective. But if patients don't have one of these types of resistance, then IV chemotherapy with carboplatin and pemetrexed said can be a very effective treatment strategy for these patients. And what we saw in the I-PASS study, which Jared alluded to earlier on is in fact, although the I-PASS study certainly showed that TKIs were a better treatment for patients with EGFR than chemotherapy.

But we also saw is that patients with EFR actually seem to do just as well, if not better, when they did receive chemotherapy than patients with other lung types of lung cancer. And so I think there's often a lot of appropriate worry and anxiety about using IB chemotherapy and its side effects. And I always try to coach patients that it is a very good tool and with modern supportive medications, patients often actually come back after starting chemo and say, you know, this isn't as bad as I thought it was going to be. And really it can work very well and patients can be on chemotherapy for quite a long time. What about immunotherapy just briefly, chemo immunotherapy is something that we sometimes consider for EGFR patients, but unlike patients who don't have targetable



alterations, the data for combinations of chemo and immunotherapy in EGFR positive lung cancer is quite limited. And in general, we know that immune checkpoint inhibitors alone have shown pretty disappointing responses, to be honest among patients with EGFR up until now.

We know that it's unsafe to give immunotherapy with EGFR inhibitors, especially with osimertinib because of high rates of pneumonitis when they're given together and even patients who receive an immunotherapy and then go on to osimertinib. For example, let's say you stop osimertinib, go onto chemo and immunotherapy. If you were to use osimertinib again, after stopping the immunotherapy, there is data that suggests that there's a higher risk of side effects and in particular pneumonitis or lung inflammation in that situation. And so I think for all of those reasons, until we have more data, I generally don't use combinations of chemo and immunotherapy for my patients who progress on osimertinib. I often will use chemotherapy alone. And as I've shown in the last bullet point here, one thing I do sometimes consider is depending on what's going on with the patient, for example, if they had brain metastasis as initial diagnosis, and those have been well controlled on osimertinib but other sites of disease might be progressing.

Sometimes we will actually do osimertinib together with chemotherapy to try to help maintain that good brain penetration of osimertinib while adding another agent. And that's something that is being studied in some upcoming trials. But finally, just to mention, you know, there are many clinical trials being done in this space, and I think many will be needed. The Orchard study is one that I think has a design that we hope will be very informative where patients undergo a biopsy after progression for osimertinib. And then based on resistance mechanisms can either go into one of these matched arms where we're actually targeting resistance mechanisms. And then those patients who don't have a biomarker that we identify can go on to various other experimental treatment arms. And we hope this will help us identify treatments for both patients with targetable resistance mechanisms and those without, so this is definitely a trial to keep an eye out for.

So, in summary, you know, resistance osimertinib is a big challenge and we still have a lot of work to do. For patients who progress on osimertinib, I think local therapy for oligi progressive limited progression of disease is important. Biopsies are important. And if possible post osimertinib therapy should be guided by resistance mechanisms, but for most patients now, you know, I think either chemotherapy or referral for clinical trials is my preferred approach. So with that, I will end and put up a beautiful picture of what you would see if you were in Boston today.

