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Examining Insights into Acquired Resistance:

The Role of Repeat Biopsies

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Dr. Pasi Janne: Good morning, everyone. My name is Pasi Janne. I'm from the Dana-Farber cancer Institute in Boston, Massachusetts. I run our thoracic oncology program here at Dana Farber. And I'm also a Professor of Medicine at Harvard Medical School. Today I'm going to discuss with you some insights into acquired resistance, and I will talk a little bit about the repeat biopsies, and also some general concepts of how we're trying to approach acquired resistance when that occurs in individuals treated with our targeted therapies. These are just disclosures. So I wanted to start out with first with some definitions of drug resistance. I think we sometimes lump drug resistance into a broad category, but I think it's helpful to try to understand some of the differences in resistance when they happen, because I think our approaches to that are also different. So let's go through these. So for example, De novo resistance, or primary resistance as this is sometimes referred to.

So, someone who would be expected to respond to a therapy that doesn't so someone who has a RET alteration, as you've just heard from Dr. Raez and is treated with a RET inhibitor, but doesn't respond to therapy. Clearly, there's a disconnect there between having the right genetic alteration and the response. And sometimes we have an understanding of why that happens, but not always, probably the most common

category that we talk about and think about is acquired resistance, meaning that regrowth of a cancer following an initial clinical benefit. So someone who has one of those dramatic radiographic responses that you saw earlier this morning, but ultimately develops regrowth of their cancer while on the drug. And that's typically what we're talking about when we talk about resistance. There are other categories sometimes we talk about a state called drug persistent disease. So somebody has a dramatic response to a targeted therapy or immunotherapy, but the disease doesn't completely go away.

There's still a portion of the cancer there that's present even while you're being treated with the drug. And this is what we often refer to as persistent disease. And this may be again, functionally and biologically be quite different. And finally pharmacologic resistance, not all of our therapies, including many of our chemotherapies and even immune therapies. And even some of our targeted therapies can access all sites in the body. And the brain, or the leptomeningeal are certainly one such area one can have a tremendous therapeutic benefit systemically, but can develop disease progression in these parts of the body. Not because the drug is not working, but the drug can't get into that location. And again, thinking about strategies and identifying drugs that have the ability to cross the blood-brain barrier. Unfortunately, many of our newer generation targeted therapies achieve that goal. But this is yet another type of category.

Now we talk a little bit about liquid biopsies and tissue biopsies, and I made this table to kind of compare and contrast, and I would agree with Dr. Weiss that these are complimentary approaches. So, but let's look at some of the potential differences. So can we do these in everybody? So tissue biopsies, no. Some sites are impractical to biopsy, some sites are unsafe to biopsy. And then I think that is a consideration. Liquid biopsy you can do in everybody because you can draw blood in everybody, however, sensitivity of these varies. And it depends a little bit on where the disease is located in individuals, for example, where disease is located predominantly in the thoracic cavity. But not elsewhere in the body. The sensitivity of these types of assays is lower. Somebody who develops progression of disease on a therapy where that progression is predominantly in the brain or in the left of an NGS, the sensitivity of one of these liquid biopsies is lower.

So again, one needs to understand that. We mentioned histology, of course, you can get histology from tissue biopsies, and I'll show you some examples of why histology may be important, and we can't get that from liquid biopsies. And of course, when you can't do histology, you can't do those protein based analyses, PD-L1 expression and others. What about time to genotyping results? And here, there are some differences, of course. The tissue biopsies if you were doing sort of next generation sequencing where you look for lots of different genetic alterations, you know, this is the weeks, two to three weeks. Specimen also needs to undergo pathology processes first. So the pathologist have to

say, yes, this is cancer. There's, you know, they've looked at the appropriate sections and then those have to be sent for analysis at a next-generation sequencing laboratory either locally or in a send-out type of fashion. From a liquid biopsy, it depends a little bit on the assay.

If you're looking for a single genetic alteration, if you're looking for EGFR T7 90 M or a single EGFRs alteration or single ALK point mutation, some assays are quite quick that are just looking for those, and you can get a result in 24 to 72 hours if one uses next generation sequencing again these take usually been around the ballpark of 10 days, a little bit faster promotes of the places than tumor-based sequencing. But still you know in the 10 day period what about the evaluation of resistance heterogeneity? This was brought up earlier it's limited in the tissue analysis because you are biopsying one site. So there are pros and cons of that. Whereas liquid biopsy can be a such a broader analysis, and really is perhaps a summation of resistance mechanisms, assuming that all of these resistance sites equally contribute to the DNA that is found in the in the blood. And finally, what is the sort of getting down to the analytical aspect, what is the depth of analysis that we can do?

So most if you're doing these next generation sequencing assays, most of the tumor-based assays are querying hundreds of genes, four to 600, depending on the analysis. So you find known things and you can find unknown things. You look for things that you may not have previously appreciated, have anything to do with a particular type of cancer or resistance mechanism because of the breadth of the analysis. Now most liquid biopsy, next generation sequencing assays are more limited. They're typically less than a hundred genes, and you find the common things. You find things that we know about, but some things are particularly difficult to find. For example, we just heard from Dr. Raez about Entrik alterations. These are typically not found on liquid biopsies, and that has to do with the technical aspects of, of the assets themselves, and how much of the sequencing would need to be contributed to finding a TRK rearrangement.

So again, it's good to know about some of the differences that you find in these types of assays. So I wanted to, again, highlight some of the practicalities of doing tissue based studies of required resistance. And this is from a study that we published a few years ago. This is a study of treating patients with Erlotinib as first-line therapy for their EGFR mutant lung cancer. And in this study, we prospectively set out to study mechanisms of resistance. And I think the findings sort of illustrate the feasibility of doing repeated biopsies. Now, the caveat here is of course, that these are done in a single center where we have access to people who can do biopsies, radiologists who can do or interventional radiologists who can do biopsies or surgeons who can do biopsy. So you have to sort of take that with a little bit of a grain of salt. So in this study, 44 patients developed acquired resistance and 35 of them were able to undergo a repeat biopsy, in about 80%.

So, if you look at why some of those other individuals were not able to undergo biopsy, it wasn't clinically feasible in some individuals or the patients refuse to undergo a biopsy in the minority of individuals. And of those 80% that underwent a biopsy, 11% had insufficient tissue. And I think a challenge for us you know, in the real world is that we think we know what the right area is to biopsy, but sometimes what happens in practicality is that the tumor is necrotic, or there's lots of dead tissue or there's fibrosis, and you don't have sufficient material there to do the types of analysis that you want. If we look at the timing here, again, a critical component, as we think about next therapies, how long did it take to get a biopsy from the time, now that the resistance was determined by the treating physician and the median time here is 12 days. And the bar graph shows the individual patients and the time to repeat biopsy, but you can see it ranges from being able to do it immediately to almost three months later.

So again, lots of variability here and in this population of individuals, the biopsy guided selection of the treatment in the majority, and about 75% of individuals here, either using, since this was a first-line Erlotinib study, either a second-generation drugs or therapy for small cell lung cancer. So let me highlight some examples to show this, and this is just to show resistance mechanisms that can happen to first-line Osimertinib therapy, and not to belabor the details, but I think the just you get a sense that there's many different ways, and we are not smart enough to figure out from the initial biopsy which direction the cancers will evolve to. This is an evolutionary process in result to a pressure of drug treatment. And it can pick out many different ways to develop resistance. And I think in the Osimertinib frontline therapy here, also there's not one dominant mechanism, resistance, everything is you know, sort of the, at most about 50% of individuals.

And hence, you know, doing a comprehensive analysis to look for resistance, as opposed to just looking for one such mechanism. I think also makes sense as I've just alluded to by the two different mechanism. And the other Point is again, getting to that heterogeneity is that this is another way of looking at that, in all of the across sort of horizontally. These are all different patients and vertically are the different resistance mechanisms. So in this, what I wanted to highlight here is that in this analysis about 15% of the patients had concurrent resistance mechanisms simultaneously. Meaning that one part of the tumor can involve in one direction and the second part of the tumor, or second independent lesion can evolve in a different direction. And I think we don't completely understand how common that is or how frequently that happens, but at least provide some information that it can happen. And I think adds to some of the complexity as we're thinking about next generation treatments.

What about from the tissue analysis? So this is now again, osimertinib resistance mechanisms from tissue analysis from a recent study published by our colleagues at Memorial Sloan Kettering. And I think you can appreciate a couple of different things. Of course, when you have histology analysis, you can look for things that happen at the histologic basis. So squamous cell transformation and small cell lung cancer transformation. So state changes in the cancer have been described, and we can, and they're sort of highlighted in these yellow pieces of the pie here. Both when Osimertinib is used as frontline therapy and as later line therapy. And then in blue and green, you can see sort of blue are new EGFR mutations and in green are other mechanisms of resistance that don't involve EGFR itself. And again, you can see the proportions here in the first and later lines of therapy. I think what's important here is that we sometimes go through this entire process either from the plasma or from the tumor.

And we end up in the gray piece of the pie, which means we don't totally know what the mechanism resistance is, or we haven't captured it, or the cancers develop resistance in a way that it's not through a genetic alteration, which was what we're capturing by these assays. And we're left with trying to understand what to do in that circumstance. So, despite all the new technology, we still do have some limitations. So what about sort of approaches to treating resistance? Again, I think these, these vary a little bit on the types of resistance. So I think the first question often is, is there a single site of resistance versus multiple sites of resistance, oftentimes for a single site of resistance, we think about local therapy, be it radiation therapy or surgery when multiple areas of resistance happen we then start to think about systemic treatment to treat the multiple sites in general. We'd like to target the targetable. If you have a secondary mutation to a targeted therapy, as you heard again from Dr. Raez about the RET example, we switched to another drug that can overcome that secondary mutation.

Sometimes we add a second drug. So, I also an example of that, of adding a second drug to an FGFR inhibitor to overcome a specific RET mechanism resistance. What if you, what if you are in that gray piece of the pie where there's no specific resistance mechanism, we've done the analysis. There's no histologic transformation. There is no genetic mechanism. And I think here, we're starting to think about, are there mechanism, agnostic treatment strategies, and I'll show you a few examples of that. And ultimately chemotherapy is one that may play a role here depending on whether or not the individuals received chemotherapy. So this is example, of two clinical trials where a second agent a MET inhibitor was added to an EGFR inhibitor on the left-hand side to Osimertinib, on the right-hand side Gefitinib. And you can see that in patients who have this particular alteration, you can have evidence of clinical benefit. You can see tumor shrinkage across the board.

I think when you delve into the details here of how do you define MET amplification, it gets much more complicated. So on the bottom left is the definition of how that was defined. And you can see that it's not a yes or no answer. It's not a mutation was present or absent. There are guidance's as to how many tumor cells do you have to analyze, and what do you need to see? And similarly, in the, in the bar graph on the waterfall plot, on the right it's color, coded based on copy number gains or immunohistochemistry. And so, for some of our resistance mechanisms, the definitions are also not quite straightforward. And I think this highlights the example, but also highlights the example that there can be clinical benefit if you identify those particular mechanisms. So finally, let me just turn into, I think some of our newer approaches or one additional approach to targeting resistance, and that is to target resistance or target cancers that are resistant, but not, but using these resistance mechanism, agnostic strategies.

And here two examples, both involve antibody, drug conjugates, and both are meaning that these are antibodies that are linked to what are kind of a chemotherapeutic agents for the time being. They bind specific proteins found on tumor cells and then internalize that antibody into the tumor cells, release the toxin, and are that way delivering targeted chemotherapy to the tumor cells. So for EGFR lung cancers, here are the we're taking advantage of the fact that EGFRs are a family in many of these other family members are also present in cancers, including HER3. And interestingly enough, HER3 is a family member that is not a known resistance mechanism to EGFRs inhibitors, unlike HER2, which is a known resistance mechanism amplification of HER2 can happen. And so that led to the idea of using this particular antibody drug conjugate called U3-1402. On the left-hand side, showed the sort of a drug antibody linked to a drug in which you can then deliver specifically to cancers to be effective.

And on the right-hand side, just some data from mouse models using patient derived, xenografts whereby we're delivering in red the drug or in blue, the control on the left-hand side the tumor that doesn't express HER3, which is one of the outliers and the drug is not affective. And on the middle and right, two examples where the drug is being delivered pre-Clinically and these have different resistance mechanisms. One model is our Erlotinib resistant cancer and the second is an Osimertinib resistant cancer, and it happens to work. Now, this has been taken forward to the clinic, and this is a presentation from last years WCLC conference by Dr. Yu. And this will be updated again at the ESMO meeting, which is coming up in a couple of weeks, to show that this does work clinically and that there are patients do respond. And I think in the bottom, if you look, we've sort of layered out the EGFR mutations, as well as the different resistance

mechanisms. And you can see that whether a individual had MET amplification or C797S or HER2 mutation or pediatric kinase mutation, there is shrinkage here.

So, this can be a strategy whereby if you don't have an option of getting a targeted therapy or one doesn't find a mechanism resistance, then this remains an approach that is still sort of tailored towards in this case EGFR mutant cancers because they express HER3. And finally, the second such drug that's entering the clinic where there's been data is another antibody drug conjugate against a completely different protein. This is called TROP2, and it's a intracellular calcium single transducer protein, but it just happens to be present in many lung cancers. And this drug, again, the same idea, antibody bound to this drug has been tested clinically in a broader arrange of individuals with lung cancer. Not just patients who have targetable alterations. Then on the right-hand side, you see the waterfall plot that was presented by Dr. Lewisburg from ASCO this past year. And you can see that again, there's clinical activity of this drug. There are patients tumors that shrink, and including in patients that have EGFR mutations or ALK rearranges. So both sort of for the targetable and the non targetable, unlike the HER3 one, this is much broader approach, not specific to one particular genotype.