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General Non Small Cell Lung Cancer

Emerging Molecular Targets in NSCLC: RET Fusions

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Dr. Joshua Bauml: My name's Josh Bauml, I'm an Assistant Professor of Medicine at the Perlman School of Medicine at the University of Pennsylvania. I'm excited to talk to you today about new updates in RET translocations in non small cell lung cancer. So, first of all, it's important to understand what a translocation is. So in DNA, in your genes, you have a series of molecules called nucleotides. So they can go one, two, all the different ones in order, but you have those on multiple chromosomes. What a translocation is, is when a piece of one chromosome breaks off and then attaches itself to another one. This is different from a mutation. A mutation is when you have that string of molecules and one of them changes, maybe it's deleted, maybe it's added, this is different. So in a translocation like we have in RET, one part of one chromosome connects to another.

The reason it's called a RET translocation, is that one of those pieces involves a gene called NET. Now the other piece can be any number of other genes. The most common partner for RET translocations is a gene called KIF5B, but there are also other ones. And this was initially relevant when we had a lot of not very active RET inhibitors, but now we have much more active drugs. In terms of when we tend to find RET fusions or

translocations. These can be seen in papillary thyroid cancer, that's a most common type of thyroid cancer or in non small cell lung cancer, but they can be seen in a wide variety of cancers. So in lung cancer, this is one to 2% of non small cell lung cancers, but it can also be seen in around 2% of ovarian cancer. So it's a wide variety of tumors.

Now, if we think about this, historically, our RET inhibitors were derived from another disease called medullary thyroid cancer, which doesn't have RET translocations, it actually has RET mutations, and those drugs were quite toxic and not very active in RET fusion, positive cancers. But now we have two drugs that are highly active in this disease. One of them recently was granted FDA approval. That drug is called Selpercatinib. And there was recent data presented ASCO, which showed that most patients who receive this drug had their cancer get smaller. Their response rate, meaning the amount of patients whose cancers got at least 30% smaller, was 85% in patients who had not received a prior treatment. Interestingly, this drug also was associated with responses in the brain. So of patients who got this and had brain metastasis, about 82% of them had the cancer in their brain respond. And that's really quite impressive. There's another drug, which is being developed in parallel, and I would expect it should be approved quite soon called Pralsetinib.

This one similarly shows a very impressive degree of response with about 66% of patients who had never received treatment, having a response. And again, Pralsetinib is associated with responses in the brain. In terms of side effects that we worry about with these drugs. It's pretty consistent across the two that one of the major side effects is high blood pressure. And so it's something that you need to talk to with your doctor to try to determine if your blood pressure is rising higher than it was, if you need to start a anti-hypertensive drug. Outside of that, the main side effect we tended to see was asymptomatic meaning without any symptoms liver enzyme numbers. So the liver numbers would go up but you can modify that. And patients did not get too sick as a result. This is a huge advance for patients that now we have access to the Selpercatinib, because this is a highly, highly active drug in a real population of patients with lung cancer. And so this is a huge advance for our patients. It controls disease, systemically. It controls disease in the brain, and it's really a great advance for our patients.