# Lung Cancer Video Library

# General Non Small Cell Lung Cancer

## Emerging Molecular Targets in NSCLC: MET

**Joshua M . Bauml, MD**

**Assistant Professor of Medicine**

**Perelman Center for Advanced Medicine**

**University of Pennsylvania**

Dr. Joshua Bauml: Hi, my name is Josh Bauml. I'm an Assistant Professor of medicine at the Perlman School of Medicine at the University of Pennsylvania. Today, I'm going to talk to you about MET Exon 14 skipping mutations. Now this is a little bit different than some of the other alterations that we've described. If you look at the DNA in yourself, it's divided into two types of portions. So one is called Exons. Exons are the business end of the genes. That's what actually codes for the protein that makes your gene do what it needs to do. But in between those Exons are little direction sections. Those are called Introns. They guide the cell in terms of figuring out when to turn the gene on, when to turn the gene off, and they guide other functions as the gene interacts with yourself. But before you actually have the gene expressed into a protein, those Introns need to be removed.

It's like when you buy something new and it has that little sticky stuff on it, and you got to peel that off. So it looks the way it's supposed to that's what's happening here. The Introns have to be what's called spliced out, but sometimes that process where the cell removes the Introns can get messed up. It can make errors. And that's what happens in a MET Exon 14 skipping alteration. The DNA gets modified in such a way that instead of removing just the interferons, this MET Exon 14 also gets removed. And so there's lots of ways that this can be detected, sometimes if the next generation sequencing panel or

the test that's being done by the oncologist and the pathologist looks at the Introns, it can find them. That's really hard for those tests to do because the tests were really designed to look at the Exon. So look at the business end of the genes.

So another way that this can be found is on what's called a fusion assay. This assay uses, instead of the DNA, it uses the RNA that the DNA gets converted into. So basically looks at it after all this splicing and prepping has happened and says, does this look right? And if you do that on a patient with a MET Exon 14 skipping alteration, what the test will see is it'll say is NET Exon 12, NET Exon 13, and then it goes straight to NET Exon 15, and the test can look at that and say, aha, Exon 14 was skipped here. It's important to talk about this testing because if the testing that has been done is not specifically looking at the Introns or it's not looking for this type of fusion, so to speak, it will miss this. And it's really important to look for this because this occurs, you know, about the same frequency as ALK, about three to 5% of the time.

There are some tumor types that have a much higher frequency, specifically sarcomatoid carcinomas, which can have up to 20 to 30% incidents of NET Exon 14, skipping. NET Exon 14 skipping was historically treated off-label with a drug called crizotinib. Crizotinib, you may know is an ALK inhibitor, and it has some efficacy here. So the response rate is about 33%, but there are a couple of problems with using crizotinib in this space. One, that response rates not as good as I'd like it to be, if we compare it to other targeted therapies, it's lower. And second of all, crizotinib does not have a good ability to get into the brain. So recently there was a new FDA approval for a drug called capmatinib. Capmatinib has a higher response rate. So in patients who had not received prior treatment capmatinib was associated with a response rate of 67.9%, and around 40% in patients with prior treatment.

Importantly, capmatinib does have the ability to penetrate into the brain. So it was very good news for my patients. When we have a new drug that's available, it's now FDA approved for patients with MET Exon 14 skipping, that overcomes those two barriers has a higher response rate and can get into the brain. There's another drug that is also being developed in this space which has had recent presentations. And that is called tepotinib. Similarly tepotinib had a pretty good response rate higher than we expected with, higher than we saw with crizotinib, with a response rate of about 46%. So a little bit higher. And this drug also seems to have efficacy in the brain. So it's exciting that we're having two new drugs for a target. One of which has already reached FDA approval, the other, which hopefully will do so quite soon. So this is a very important target that we need to make sure we are looking for in our patients with metastatic lung cancer, especially those with sarcomatoid carcinoma.