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The Molecular Mechanisms of HER2 Mutations Driving NSCLC Disease Progression

Announcer:
Welcome to *Project Oncology* on ReachMD. This episode is sponsored by AstraZeneca and Daiichi Sankyo. Here's your host, Dr. Hector Chapa.

Dr. Chapa:
This is *Project Oncology* and I'm Dr. Hector Chapa. Joining me to examine HER2 mutations as a driver of disease progression in non-small cell lung cancer is Dr. Sandra Misale. She is Research Associate at Memorial Sloan Kettering Cancer Center. Dr. Misale's research focuses on the connections between genetics and molecular pharmacology to develop personalized cancer therapy. Dr. Misale, welcome to the program.

Dr. Misale:
Thanks for having me.

Dr. Chapa:
Well, let's start off with some background on HER2 mutations. Dr. Misale, what are some key molecular features and pathological characteristics that define these genetic mutations?

Dr. Misale:
So, more in general, HER2 is one of the four members of the HER family. These are tyrosine kinase receptors that have formed ligand binding and memorization; any shape of signaling cascade that can modulate the preparation's survival. So, in many tumor types, including non-small cell lung cancer, these genes are encoding for proteins that are a little bit different from the normal. These differences can be due to genetic alteration that causes mutation, or gene amplification, so having many copies of the wild-type normal gene. The HER2 mutations can occur in different places and different parts of the genes, and usually are falling in the extra cellular domain or in the kinase domain of this receptor, but also in other parts of the gene that are also very frequently happening in non-small cell lung cancer.

Dr. Chapa:
Now you mentioned the two ways that this mutation presents: overexpression and amplification. How do these differ, one from the other?

Dr. Misale:
So, the amplification is the result of a high expression of the normal HER2 receptor. So, at the DNA level, we don't have only two copies as is normal, of the HER2 genes, but we have multiple. That means that this gene can get transcribed many times, and at the end of the day, the cell presents a very high number of these receptors on the membrane.

But this receptor is still wild-type, so they are supposed to signal the same way as in the they signal in the normal cell, but the amount of signal is very high because we have many receptors. On the contrary, the mutated receptors are expressed at the normal level, but this mutation causes this the HER2 receptor to be consistently active. So that means, that the signaling that HER2 promotes, so that proliferation cell survival it's always sustained and never gets stopped, so cancer cells can continuously proliferate.

Dr. Chapa:
Now I wanna explore this a little bit more. Can you tell us some of the different variations of HER2 mutations in patients with non-small cell lung cancer, and their clinical magnitude?

Dr. Misale:
Yes, so overall, I want to remind that HER2 is mutated in around 4 percent of non-small cell lung cancer patients, and that means that it's not a very, very frequent genetic event. But although, even if it's in small population, we have many different mutations that can occur in the tyrosine kinase domain, and in this part of the receptor. It falls close in the cell membrane, it's called juxtamembrane. But also, we see, or we have treated patients with a mutation on the extracellular domain, too.

Dr. Chapa:
Well, now that we have an understanding of these clinical features, and the characteristics of HER2 mutations, can you tell us about how they drive disease progression?

Dr. Misale:
So, in general they both drive disease progression in a similar way. The big difference is how we can target, because in general both the alterations, so, having many copies of HER2 on cell surface, or normal amount of copies, but very much active. This, in both cases, drives tumor growth. But what is the effect and we can, use against the tumor in these two different settings is actually very different.

Dr. Chapa:
For those of you just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Hector Chapa, and I'm speaking with Dr. Sandra Misale about HER2 mutations in non-small cell lung cancer. Now, Dr. Misale, if we turn our attention to treatment, what are some current therapeutic options for patients with HER2 mutated non-small cell lung cancer?

Dr. Misale:
So, in general, these patients are still treated with chemotherapies, but many targeted therapies are actually in clinical trial right now. And possibly many of them will be approved very soon. In this group we have two class of drugs one is the tyrosine kinase inhibitors. Usually irreversible tyrosine kinase inhibitors, like neratinib or afatinib are used for the treatment of these patients. And on the other hand, we have antibody drug conjugates, so the antibodies that can also carry specific chemotherapy attached to, and basically when they bind the HER2, this antibody and the chemo gets internalized together with the receptor, and the chemotherapy gets released inside the cells, and eventually kills the tumor cells. So we have a sort of targeted chemotherapy with this drug.

Dr. Chapa:
And just to bring all of this together, before we close, Dr. Misale, what can you tell us about biomarker testing, how it's impacted the way we treat HER2 mutated non-small cell lung cancer?

Dr. Misale:
So I firmly believe that biomarker testing is the key for the success of modern oncology. Genetic testing is pivotal for the success of HER2-targeting therapies, but also for all the targeted therapies. In parallel you know, assess doing genetic testing and biomarkers, we also would need to expand the knowledge of molecular mechanism and their response to pharmacological targeting. That is also extremely important to better understand response and resistance to anti-HER2 targeted therapies.

Dr. Chapa:
Well, with those comments in mind, I wanna thank my guest, Dr. Sandra Misale, for joining me to take a look at the molecular mechanisms of HER2 mutations in non-small cell lung cancer. Dr. Misale, it was great having you on the program.

Dr. Misale:
Thank you so much.

Announcer:
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