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HER2 Mutations in NSCLC: What You Need to Know

Announcer:
Welcome to *Project Oncology* on ReachMD. On this episode, sponsored by AstraZeneca and Daiichi Sankyo, we're joined by Dr. Alexander Spira, who's the Co-Director of the VCS Research Institute, Director of the Thoracic and Phase I Program, and Clinical Assistant Professor at Johns Hopkins. Dr. Spira is here to share an overview of HER2 Mutations in NSCLC. Let's hear from Dr. Spira now.

Dr. Spira:
HER2 mutations are a relatively newly understood entity. They are relatively uncommon, only making up less than 5 to 10% of lung cancer patients. They're newly understood and very distinct from what we think about in other malignancies, such as the breast cancer world where we have HER2 amplifications by either IHC or FISH. They're only detected based upon testing with things such as next generation sequencing or other PCR-based testing. So they are relatively rare and relatively newly understood as of now, but they have emerged as a new biomarker with new targeted therapies directly against them.

CNS metastases are relatively common in patients with HER2 mutated non-small cell lung cancer. We know that brain metastases can occur in anybody with lung cancer, of course. We've seen that for many decades. There's nothing new and special about that. But CNS metastases do happen at a higher frequency, both at diagnosis as well as over time. And the reason that's important is as we develop new drugs that target HER2 mutations, –it would be great if we could have those drugs that specifically have central nervous system penetration. Obviously, that's an extra thing. We just want drugs that are active. But it's super important to think about that because as we know, brain metastases and CNS metastases can drastically change the course for our lung cancer patients.

Turning our attention now to prognosis and current therapies, current therapies are very limited. As we all know, in the world of lung cancer, the world has changed dramatically over the last decade, if not more, with the advent of targeted therapies. And currently, patients with a specific mutation, that's what's called a driver mutation, of course, for the lung cancer, makes up almost half, somewhere in the 40% range, of patients with non-small cell lung cancer. When you look at HER2 mutations, there are currently no approved therapies. But again, there are some emerging right now that can help target and treat those patients. The outcome of those patients, of course, is worse. They tend not to respond to chemotherapy, which is the standard therapy. And of course, we all know that when you have a biomarker, and you can target that biomarker for a patient's lung cancer journey, that of course is better, not only will it open to alternative therapies, but as we know, biomarker-driven therapy tends to be easier, better tolerated, and tends to last longer.

In terms of these HER2 mutations, they don't tend to overlap with other oncogenic drivers. In other words, they don't tend to be seen in conjunction. Now they can be seen in conjunction over time. For example, if you put somebody on EGFR-based therapy, it's not uncommon for them to develop a secondary resistance, although there's a lot and they are rare. But they tend not to overlap with other oncogenic drivers, meaning you need to look for them, most importantly. So I like to give the example: you can't treat somebody with a targeted therapy if you don't look for that targeted therapy. So it's super important to look for them and look for them independently of other oncogenic drivers, be it KRAS, EGFR, ALK, or any of those.

What's going to be really interesting is as the field evolves over time is that we do know that patients who've been on one targeted therapy often develop a secondary resistance with some of these other mutations, including HER2. So some of the things we need to do is look in parallel, how do you combine drugs over time as well.

Finally, let's look at some of the key characteristics of some of these patients with HER2 mutated non-small cell lung cancer. They tend to smoke less, they tend to be non-smokers, they tend to be a younger population as well. So of course, all our lung cancer patients are important. But these are a younger population that often can tolerate several different rounds of chemotherapy, most importantly, can

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also even enroll in clinical studies. And this is important as we think not only about the design of the studies, but as the population we're targeting as well. It's not uncommon, we still see this is that in many parts of the country, they don't see a lot of patients with targetable mutations because they still have a large number of smokers, so that dominates their treatment paradigm. For us, we actually see more non-smokers than smokers. So they're really driven by these patients with specific driver mutations. So it's important to think about that.

Everybody, of course, should be checked for these driver mutations: HER2, EGFR, what have you. But it's important to think about this as a new emerging one because there are no approved therapies right now, but hopefully, there'll be some shortly in the future and there's obviously some ongoing clinical studies. If you didn't check for HER2 mutation because your panel was limited before, please don't forget. Go back. Make sure you look at their panel. It's why I always think about next generation sequencing panels as being very all encompassing and look for everything, not only the ones that are here now, but also mutations that might be present in the future due to new drug development.

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