



Lung Cancer

General Non Small Cell Lung Cancer

Emerging Molecular Targets in NSCLC:KRAS

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Dr. Sandip Patel:

I'm Sandip Patel, a medical oncologist, and associate professor at the University of California, San Diego, where I mainly focus on early phase clinical trials and thoracic oncology. I'm honored today to be discussing some very important innovations that are happening in the clinical trial space that are imminently about to be available more broadly in clinic. And they're still available in clinical trials for patients. The first topic I want to talk about today is KRAS mutations in metastatic non small cell lung cancer. KRAS is an area in which the federal government has invested hundreds of millions of dollars, given that's one of the most common mutations that happen, not only in lung cancer, but multiple other cancer types as well, including pancreatic cancer and colon cancer among others. Now it turns out the fruits of this labor have recently born, in the sense that there are some small molecule inhibitors that have been developed that target a specific mutation called KRAS G12C.

Now this may sound like it's a very rare, nuanced finding, but in fact, almost half of patients with non small cell lung cancer with KRAS mutations will in fact, have a KRAS G12C mutation. And moreover, if you look at the total number of patients in the US who may have this mutation, it's about 25,000 patients, which is equivalent to the entirety of the number of patients with brain tumors, for example, which is a substantial subset. And so taking a step back any time you're fighting cancer, you always have to make sure to understand which questions are most meaningful to ask to help you or your loved ones. And one of the most important is what's making my tumor tick? What's the molecular basis of my cancer? And so if you have a tumor in particular metastatic non-squamous non small cell lung cancer. So those things like lung adenocarcinoma, for example, the question on which mutations are fueling the cancer is key. And it's a



question that needs to be answered before any immunotherapy is administered in particular.

And ideally before any therapy is if there's a window, and a safe window to wait for these molecular tests, because all of these great drugs that are out there, we don't know that patients are candidates for them unless they have appropriate testing. And so

the modern era, if you're looking for multiple genes in terms of making an appropriate molecular diagnosis for a patient, if you've metastatic, non-squamous non small cell lung cancer, there are many genes we need to look at EGFR, ALK, ROS1, MET, RET, BRAF, HER2, NTRAC, and the list goes on. I think KRAS is one of them now. And the nature of the KRAS mutation, the nature of the EGFR mutation is important, but then how do you go looking for this? You can't look at this under slides, you need a DNA level test, and that's what next generation sequencing allows. And this can be done in tissue, or it can be done in two tubes of blood by cell free DNA or liquid biopsy. And so once you've had the appropriate molecular testing done, and if it comes back with a mutations such as KRAS G12C, there are a couple of opportunities.

So there are clinical trials looking at these small molecule inhibitors. There are two that are currently in clinical investigation that are lead compounds, one by Amgen and one by Morati, that are specific inhibitors for G12C. These are small molecule pills that actually get at the underlying biology. And it seems almost half of patients can have a response to this in terms of tumor shrinkage with lung cancer, though, it seems to be unique in some other cancers like colon and pancreatic cancer. The responses are not as durable depending on which drug and which setting you're talking about. But the other point is that many patients with KRAS mutated metastatic, non small cell lung cancer have that mutation because of a smoking related history. And in fact, chemo, immunotherapy, or some combination of immunotherapy may be their best therapy. And so once these drugs are more widely available, even if you have KRAS G12C as a target, one of the nuanced discussions that's going to have to occur is whether immunotherapy or chemo immunotherapy is your best option.

Given that some patients can have responses that last years with immunotherapy, with that mutation or a targeted therapy pill, where we don't yet know how durable those responses are. And so there are many questions we still need to answer, but we can't answer them if we don't do the appropriate testing. And for patients who have progressed and had growth of their cancer after chemo immunotherapy, and other standard therapies, if they have a KRAS G12C mutation, I would highly recommend they seek out one of these clinical trials as these drugs appear to be efficacious. And our hope is they're efficacious for a longer and longer period of time for our patients. But we can't get the patients on the appropriate therapy for them. And unleash the promise



of precision medicine and personalized medicine, if we don't know that that mutation exists. And so that's why doing the appropriate molecular testing and making that molecular diagnosis is so important.