Lung Cancer

General Non Small Cell Lung Cancer

Emerging Molecular Targets in NSCLC: EGFR EXON 20

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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. Now I'll be discussing EGFR Exon 20 insertion mutations. Now I want to be very careful of this discussion because it sounds like a lot of the other mutations that patients have. So EGFR mutation or what's many refer to as a canonical EGFR mutation occurs in about 90% of patients with that EGFR mutation. And that is an Exon 19 deletion or L858R and Exon 21 mutation. Those two represent 90% of mutations with an EGFR. So we're talking about a subset of a subset here, but amongst the 10% that remain in terms of EGFR mutations, there's something called an EGFR Exon 20 insertion.

So that's one way we got to be careful in terms of defining this tumor and naming that tune is understanding the complex nomenclature that underlies this entity. The other is that EGFR and HER2 are part of a super family, their cousins, and HER2 actually also has Exon 20 insertions for which there's some unique HER2 targeting drugs available. And so the first important thing is we got to name the tune here. And so EGFR Exon 20 insertions are not those traditional EGFR mutations, Exon 19 deletions, and L858R, and they're not these HER2 Exon 20 insertions, they're their own unique entity. And so one of the hard parts about precision medicine and molecular guided medicine is really defining what the patient is having to fight. And so here, we're talking specifically about EGFR Exon 20 insertions.

They're relatively rare mutation that happens often patients who've never smoked. And the reason this is a unique entity is that the traditional EGFR inhibitors that we're used to, drugs like orlatinib, afatnib gefitinib, osimertinib, at least at the traditional doses do

not seem to work on this specific disease, EGFR Exon 20 insertion, non small cell lung cancer. The reasons are really related to the biology. When you have an Exon 20 insertion where these drugs bind kind of flattens down, you actually need a drug with a unique geometry to kind of fit in there and break up that lock and key. And so it's key to have drugs that do that. And so there are two drugs in later stages of clinical development, the first is Poziotinib. The second is a drug called Mobocertinib. These are

small molecule inhibitor pills that bind the inside of this EGFR protein in a unique way. There's also been some efforts at looking at Osimertinib, which is a drug that's used in more traditional canonical mutated EGFR non small cell lung cancer, Exon 19 deletions, and L858R, mutations and doubling the dose to 160 milligrams.

Broadly, these approaches tend to benefit anywhere from a third to half of patients. And so absolutely these are approaches. I would seek out the question on what order these drugs should be given to patients? I think it's something that's very active in the field. I think in particular whether chemo immunotherapy is the best to use upfront or later on is an ongoing question based on some of the response data, especially we've seen with chemotherapy plus bevacizumab plus atezolizomab, ion power 150 regimen. The other point is that there's a unique drug by J and J that's a bi-specific antibody. So this is an infusional drug as opposed to a pill that targets EGFR MET. And this drug appears in about a third of patients to lead a shrinkage of tumors that are driven by the Exon 20 insertion in EGFR. And so not only do we have these small molecule pills, we also have antibodies that may help us in particular bi-specific antibodies.

And so I think the future is bright, but the key is to make sure we understand if a patient actually has this mutation, meaning they undergo appropriate molecular testing upfront, which I view for a patient with metastatic non-squamous non small cell lung cancer to be a next generation sequencing approach. So that way we can understand whether they have mutations in EGFR, ALK, ROS1, HER2, MET, and BRAF, and the variety of other mutations that are not targetable, including NTRAC, right. Which is quite rare. And with a goal of matching patients to their appropriate therapy at the right time. And so I think EGFR Exon 20 insertion has been a very difficult disease but help is on the way for patients and their caregivers with some of these new agents, whether they're small molecule inhibitors such as poziotinib, or mobocertinib, or infusional antibodies that target its biology such as the new J and J compound. And so I think other features bright, but we got to make sure to do the appropriate testing so we can give these patients the appropriate therapy.