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Panel Discussion: Options for Targeting NRG1

Announcer:
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Dr. Liu:
Hi, this is Dr. Stephen Liu. I'm a thoracic medical oncologist at Georgetown University.

Dr. Dotan:
And hi, my name is Efrat Dotan. I'm a GI medical oncologist at Fox Chase Cancer Center.

Dr. Liu:
And today, we're gonna talk a little bit about NRG1 fusions. NRG1 is neuregulin 1 and we know that gene fusions are, you know, oncologic drivers. These are rare, but important events that we see across cancers, and in my clinic, I primarily treat patients with non-small cell lung cancer. We know that non-small cell lung cancer can harbor NRG1 fusions, so they are uncommon events. Efrat, you also see these in your own clinic, right?

Dr. Dotan:
Yeah, so I treat primarily pancreatic cancer patients, and although these are very, very, very rare. If you dig deep enough, you can find them in pancreatic cancer patients and I think they're important to recognize and think about as we're treating these patients with very difficult cancers to manage.

Dr. Liu:
Yeah, this is sort of a unique target. In lung cancer, we have a lotta different targeted therapies and primarily, what we're looking at there are constitutively active kinases We're looking at mutations and fusions that lead to this receptor that's overactive. NRG1 fusions are very different because NRG1 is producing the ligand, which binds to the receptor, and it actually signals through the HER3, HER2 pathway. That's why a lot of the drugs that we're looking at as potential treatments for NRG1 fusion cancers involve HER2 and HER3 because they are part of the same very important pathway. The challenge for us, and, you know, I know that we're both involved in trials in this space really is detection, and these are hard to find for a couple reasons. One, because they're rare. They're rare to start with, but two, because not all of our biomarker tests are gonna find these the right way. You know, in lung cancer, I think in the US especially, most of us are using next-generation sequencing and people ask can next-gen sequencing find an NRG1 fusion if it's there? And my answer is maybe. My answer is it depends, right. What are your thoughts on that question?

Dr. Dotan:
I agree 100% I think there are two big issues that we struggle with. One is tissue acquisition. I think both of these diseases usually are in areas where it's not the easiest thing to biopsy. Patient sometimes has to go through multiple biopsies in order to get enough tissue so

we can actually run all the tests that we wanna run, and that's problem number one. Some of our colleagues will not push through for additional biopsies to really get all these results, but even if you have the tissue, you have to make sure that the next-gen sequencing is done in the most thorough way possible, including both DNA and RNA sequencing. So we make sure we don't miss any of these very unique and rare abnormalities, and, you know, I can speak for pancreas cancer. This is a disease with limited treatment option, very poor survival, but when you find that one patient that has this fusion, this can be life-altering and really provide treatment options that change the survival significantly. So it is worth putting in the extra effort and finding these abnormalities.

Dr. Liu:
Yeah, I think that it, you know, in the current age, it's not enough to say pancreatic cancer. It's not enough to say lung cancer, lung adenocarcinoma. We really do need to know the specific genomic signature 'cause it's a totally different biology. It should be a different treatment, and in my mind, that kind of means it's different cancer, and so if someone has a lung cancer and there's no other test, I am not equipped to make the right treatment decisions, and so then you're gonna guess, and we really don't like to guess when it comes to the treatment of cancer. So the sequencing's important. Part of the challenge here is it's not just, you know, checking a box. There are a lotta technical challenges with finding NRG1 fusions. The gene we're talking about, NRG1, not to get too technical, it's a massive gene. It's a monster of a gene. It represents 1/2000 of the entire genome just by itself. Most of that's intronic and what that means is if the next-gen sequencing platform you're using is DNA, they are not gonna have enough coverage to find an NRG1 fusion reliably. Once in a while, they might pick it up if it's a specific fusion partner, but there are so many different NRG1 fusions that if you're not doing RNA sequencing, you're really gonna miss these, and you know, some people ask can we do liquid biopsy if we can't get enough tissue and you can do liquid biopsy, do a lot of liquid biopsies, but liquid biopsy will not pick these up because liquid biopsies right now are DNA-based and we don't have an RNA-based liquid assay. So RNA sequencing really is the key, and so to our colleagues, to our patients, if they've had full profiling, they've had full sequencing, we need to be more granular than that. Was it DNA or was it DNA and RNA? Because that RNA piece is critical, and I understand it's a lot to ask because when a lot of us did our training, this was not part of our treatment, of our training. We didn't need to know these types of things, but now, we do, we need that kinda granularity, and I think it's important to, yeah.

Dr. Dotan:
Oh, I was just gonna say, you know, it is important to think about this, but also important to think about this in patients that have clues that may point us to even this type of analysis being more important. So within pancreas cancer, we know that these type of abnormalities usually occur in patients with RAS-wild type tumors. I'm sure you all know, pancreas cancer, 95% of patients have a RAS mutation. If you get next-gen sequencing and there is no RAS mutation and the patient has pancreas cancer do not stop there. There has to be some other abnormality that's driving this cancer. Check to see that RNA sequencing was done. Make sure the patient had complete next-gen sequencing and nothing was missed, and I believe in lung cancer, there are some clues that we can use as well for this kind of screening.

Dr. Liu:
Yeah, primarily, patients are non-smokers. It doesn't mean you should limit your testing to non-smokers because smoking doesn't protect you from getting an NRG1 fusion, but if you have a non-smoker with lung cancer, absolutely. If you don't find anything you have to ask yourself, did we look far enough, and look, you know, talk to your pathologist, was the sequencing done on a bone biopsy that was decalcified, which corrupted all the DNA? Was it a really necrotic sample without a lot of viable tissue? So we really need to look hard, it's critically important, and, you know, for lung cancer, we know that if you have advanced lung cancer with an NRG1 fusion, the standard treatments are not very good. You know, we did a retrospective assay, that retrospective analysis looking at outcomes in NRG1 fusion-positive non-small cell lung cancer, and if we think of our sort of most comprehensive treatment approach, a combination of chemotherapy and immunotherapy, this chemo-immunotherapy approach, in patients with an NRG1 fusion, the chance of response in our registry was 0%. No patients responded. Outcomes were very poor with standard therapy.

Dr. Dotan:
Yeah, I don't believe there's such data for pancreas, but I think the RAS-wild type is a really important clue in our disease setting.

Dr. Liu:
We think of treatment options. There are a lot of important things in development, and I think what's most important to stress is that treatments can work. We've seen responses with lots of different therapies, and so it provides a lot of hope to patients with an NRG1 fusion-positive lung cancer for afatinib, which is a pan-ErbB kinase inhibitor, an oral medicine that we use to treat lung cancer. There have been many responses reported. These are all case series. So we don't really know how frequently it works, but there are

prospective studies now being run through ASCO and through a decentralized study trying to tell us what's the chance of response with a drug like afatinib. There are also some newer agents being developed in NRG1 fusions, some antibodies, right, Efrat?

Dr. Dotan:
Right, so there are two antibodies that are currently in trial. I guess the one that has been recently, both have recently been presented at ASCO. Zeno, zenocutuzumab is an antibody that has basically two arms, one targeting HER2 and the other one targeting the binding area of NRG1, and by doing that, it prevents this dimerization of HER2 and HER3 and prevents the downstream signaling, and that study has shown significant activity, both in lung cancer, I believe there were over 40 patients with lung cancer on that trial, and almost, I think, 19 patients with pancreas cancer. So really significant amount of duration of response and overall survival that we have never seen in pancreas cancer patients who have been previously treated, and then there's the CRESTONE study that is also using an antibody.

Dr. Liu:
Yeah, and so seribantumab is a HER3 antibody that has shown some early efficacy. Both drugs have been labeled for sort of rapid development and review by the FDA and what strikes me about both seribantumab and zenocutuzumab, they're showing pretty dramatic responses in some patients with their NRG1 fusion cancers across different fusion partners, and because they are pretty specific at their targets, the side effect profile, the toxicity profile has been very reassuring. These are very well-tolerated drugs. Has that been your experience as well?

Dr. Dotan:
Absolutely, interestingly, we don't see any cardiac toxicity, which we see with prior HER2 inhibitors and then patients, I mean, really have no side effects. It's pretty remarkable to see that in a pancreatic cancer patient that is used to getting treatment like FOLFIRINOX. I mean, this is, you know, life-changing.

Dr. Liu:
So these are rare events, NRG1 fusions. They are impactful though, and it really can make a difference in the optimal management. There are new drugs in development. These are great options, and I would encourage anyone with a patient or a contact who has an NRG1 fusion-positive cancer to reach out to one of these centers. Sometimes these centers can help in terms of coordination, travel, those types of things. You know, don't worry about the barriers. Just talk to somebody about these studies. These are important studies, but there are only options if you find the fusion, right.

Dr. Dotan:
Right, and I think there are also expanded access options that you can reach out for. Really, these patients can significantly benefit from this intervention, so we shouldn't miss it.

Dr. Liu:
All right, well, thanks, Efrat, for this dialogue, and for all the work that you're doing and certainly, thanks to the audience for participating.

Dr. Dotan:
Thank you, this was an exciting conversation.

Announcer:
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