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What Are the Novel Targeted Therapies for NRG1 Fusion Tumors?

Announcer:
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Dr. Dotan:
Hello, my name is Efrat Dotan and I'm from Fox Chase Cancer Center. I'll be talking about novel therapies for NRG1 fusion tumors. Neuregulin is a ligand that binds to the HER3 receptor and promotes standardization of HER2 and HER3 receptor. And by that downstream signaling activation of the PI3 kinase, AKT, and mTOR pathways. In patients that have NRG1 fusion we see this pathway over activated resulting in constant downstream signaling and tumor growth and proliferation. And therefore targeted treatments that focus on this pathway need to block HER2/HER3 dimerization as well as the binding site for NRG1 at the HER3 receptor. I'll be talking about three such agents that are under development or already available for use. The first agent is Afatnib.

And as you can see on the diagram, Afatnib is a small molecule. It's a HER3 kinase inhibitor that causes an irreversible inhibition of this Tyrosine kinase. And multiple case reports have been published demonstrating significant activity and impressive responses in patients with NRG1 fusions. In the images you can see two patients with pancreatic cancer that had a nice response to Afatnib after a few weeks of therapy. And at the bottom, a graph that shows a nice decrease in CA19-9 level following the use of Afatnib. And here is a long list of reports showing activity of Afatnib in various tumor types, all harboring the NRG1 fusion with various different partners. The next agent is Zenocutuzumab. Zenocutuzumab, or for short Zeno, is a bispecific humanized IgG1 antibody that has a novel action in which it docks on the HER2 receptor, as well as block the NRG1 binding site on the HER3 receptor. By doing that, we prevent dimerization of HER2 and HER3 and downstream signaling. Zenocutuzumab has been published in multiple case reports. And the first one here is of a patient with pancreatic cancer.

You can see patient received prior chemotherapy and then had a very nice response, over 19 months, with a PR using Zenocutuzumab. The next case report published is of patient with a non-small cell lung cancer who has received multiple prior lines of therapies with chemotherapy and immunotherapy. Ultimately was placed on Zenocutuzumab with a nice PR of seven months. Both patients, of course, with NRG1 fusion. At ASCO this year we heard the presentation of a global phase 1/2 clinical trial using Zenocutuzumab in various tumor types harboring the NRG1 fusion. And here's the waterfall plot. You can see here, a significant response seen in multiple patients with mostly partial responses and stable diseases. But overall, the response rate was 34% for all tumor types, 42% for pancreatic cancers, and 35% for non-small cell lung cancer. All of these responses were seen regardless of the NRG1 partners.

Of total there were about 26 partners that were reported in this study and the responses were seen across the board. In addition, in terms of tolerability, Zenocutuzumab was very well tolerated with a very low discontinuation rate and no safety concerns that were raised. There was some GI toxicity, skin toxicity, mostly mild, and no cardiac toxicity was seen. The last agent I wanna discuss is Seribantumab. Seribantumab is a fully human immunoglobulin monoclonal antibody against HER3. And it does two main things. First of all, it competes with NRG1 on the binding site of HER3. And two, it inhibits the dimerization and phosphorylation of HER3 and other receptors in this family. By that we inhibit downstream signaling of PI3 kinase, AKT, MAP kinase, and ERK pathways and decrease

tumor growth and proliferation. At ASCO this year we heard the presentation of the CRESTONE study. This is a phase two trial using an anti-HER3 antibody Seribantumab in solid tumors with NRG1 fusions.

The study has three cohorts, but the main one is cohort one which includes patients who have not seen any NRG1 targeted therapies. At ASCO we heard the report of 15 evaluable patients for response and 35 evaluable patients for safety. And here's the waterfall plot for the patients who are evaluable for response. These were mostly non-small cell lung cancer patients. And as you can see, two patients actually had CR in this trial. Overall, there was a 33% overall response rate. And in non-small cell lung cancer, 36%. In addition, the disease control rate as was rated by the investigator was 92%. Of note, Seribantumab was again, very well tolerated, mostly grade one or two adverse events. And no treatment discontinuation was noted. And here are two case reports presented with Seribantumab. These are two patients with non-small cell lung cancer, both with multiple prior lines of therapy.

And as you can see, one patient had a PR and the second patient had a CR, both for quite a long time, and had a significant response to treatment with Seribantumab. In summary, I think we can see that there is significant evidence showing that novel agents are available, either under investigation or available for use for targeting tumors that harbor the NRG1 fusion. We can see that all of these treatment can provide clinical benefits, some of them with very durable responses. As well as they're all very well tolerated with limited adverse events. I think this confirms the need for routine testing that is necessary for identification of patients who are candidates for these treatment approaches and can benefit from them. I thank you for your attention.

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