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https://reachmd.com/programs/cme/patient-case-timing-and-selection-of-nrg1-fusion-targeted-eligible-patients/14343/

Released: 08/17/2022
Valid until: 08/17/2023
Time needed to complete: 59m

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Patient Case: Timing and Selection of NRG1-fusion Targeted Eligible Patients

Announcer:
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Dr. Dotan:
Hello, my name is Efrat Dotan, and I'm from Fox Chase Cancer Center in Philadelphia. I'll be talking now about a patient case and thinking about the timing and selection of NRG1-fusion targeted therapy for eligible patients. The first case is a patient that I have seen with metastatic pancreatic cancer. This woman was a 70-year-old female with metastatic disease that was diagnosed in 2017. She had a past medical history of asthma, osteoarthritis, psoriasis, and Raynaud's syndrome and was diagnosed in 2017 with evidence of disease involving her liver. At that point, she had FoundationOne testing with DNA sequencing, which showed evidence of BCOR mutation and a KRAS wild-type tumor. She was then placed on a clinical trial using a combination of gemcitabine and Abraxane with an investigational agent and was on that study for almost three years, until evidence of disease progression. At that point, treatment was started with FOLFOX, followed by a long-term maintenance on 5FU, and this lasted for almost a year, until July of 2021. In August 2021, she was placed on another clinical trial with an investigational agent until her disease progression in February of 2022.

Here are some CT images of her liver at the time of progression in February of 2022. As you can see, she had quite significant involvement but still had excellent performance status with good liver function and no significant symptoms. Her oncologist found the case to be very odd, and at the first disease progression initiated additional molecular testing, which included RNA sequencing. And interestingly, she was found to have an NRG1 fusion with a fusion partner, APP. Upon her disease progression in February of 2022, this patient was enrolled in the CRESTONE study. The CRESTONE study is a trial utilizing seribantumab. Seribantumab is a fully humanized IgG monoclonal antibody against HER3, and as you can see, this antibody blocks the dimerization of HER2 and HER3 as well as blocking the binding site of NRG1 protein. By doing that, we are able to reduce tumor growth and decrease proliferation through inhibition of the PI 3-kinase and Akt pathways. Here is the study design of the CRESTONE study, a phase two trial using the anti-HER3 antibody Seribantumab. And you can see the study has three cohorts with the main cohort of patients that carry an NRG1 fusion and have not received any other therapy. So a second case I wanted to highlight is a case that was actually published this year. This is the case of a 52-year-old man with stage III non-small lung cancer, with a mixed histology of mucinous and non-mucinous adenocarcinoma.

The patient was a non-smoker, and DNA sequencing showed no driver mutation in EGFR, KRAS, ALK, ROS-1, RET, BRAF, HER2, MET exon 14, or NTRK. RNA sequencing was also done, and in fact, it showed fusion with CD74. As you can see at the image at the bottom of the slide, this patient received multiple different treatments, including a two-month course of therapy with afatinib, which is a small molecule that inhibits the HER2 and HER3 receptors. After multiple lines of therapy, the patient enrolled on a clinical trial and received zenocutuzumab and had a prolonged PR for seven months. So, zenocutuzumab is a HER2/HER3 bispecific humanized IgG1 antibody, it docks to the HER2 and also blocks the NRG1 binding site on HER3, and by that, blocking the dimerization of HER2 and HER3 and downstream signaling. At the top of the slide, you can see the global program; it is a multicenter development program, including a phase 1/2 global study as well as an early access program for zenocutuzumab, with a prolonged followup for these patients. So, in summary, dedicated RNA sequencing can identify NRG1 fusions in tumors and can identify patients who are eligible for targeted

therapies. It is really important to insist on this type of testing and identify it in patients that have higher incidence of these fusions, including non-small cell lung cancer with invasive mucinous adenocarcinoma or KRAS wild-type pancreatic cancer. Thank you for your attention.

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