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Can My Patient Participate in NRG1-Targeted Clinical Trials?

Announcer:
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Dr. Liu:
Hello, My name is Dr. Stephen Liu. I'm the Director of Thoracic Oncology at Georgetown University in Washington, DC. This presentation is on patient participation in NRG1-targeted clinical trials. NRG1 fusions are rare, but important events that occur across tumor types. These fusions represent viable therapeutic targets, but to date, there are no FDA approved treatments. There are however, several ongoing trials investigating active agents in tumors with an NRG1 fusion. These trials are primarily tumor-agnostic designs, which means they would include patients whose cancer harbors an NRG1 fusion, regardless of what type of cancer is there. There are many challenges to these important studies. One, NRG1 fusions are rare events occurring in about 0.2% of cancers.

Two, RNA-based testing is needed for identification, and DNA-based next generation sequencing, which is very commonly used in the US, will not reliably detect an NRG1 fusion. In addition, we know from retrospective global registries in lung cancer that NRG1 fusion carries a poor prognosis, demonstrating poor outcomes with standard therapy. This is why trials featuring NRG1-targeted agents are very appealing. We do know that NRG1 fusions are actionable. And while there are no FDA approved agents, there are active agents. Afatinib is an orally bioavailable pan-Erb kinase inhibitor that is currently approved for the treatment of EGFR mutant non-small cell lung cancer. It is also active in NRG1 fusion-positive cancers. There have been multiple case reports, and case series, that have demonstrated responses. Responses have been at times dramatic, and at times durable, even spanning out past 18 months. But with case reports and case series, there is significant reporting biases. This means we report responses that all the patients who receive this drug and do not mount a response, are likely not reported at all. Until we have prospective data, we cannot speculate as to the response rate of Afatinib. Fortunately, that prospective data is being collected. The taper trial is a multi-basket study being led by ASCO; The American Society for Clinical Oncology. In tumors with an NRG1 fusion, they would receive Afatinib as part of the taper study. In addition, Boehringer Ingelheim is launching a decentralized study with single-patient INDs, where drug is delivered to patients, regardless of location, to determine the prospective response rate and safety of Afatinib in this population.

Another drug being explored in clinical trials for NRG1 fusion-positive cancers is the eNRGy trial that looks at Zenocutuzumab or MCLA-128. This molecule is a bispecific antibody that targets HER2 and HER3, and it maintains antibody dependent cell-mediated cytotoxicity. This molecule, when it engages its target, blocks the NRG1 ligand from binding to HER3. This prevents that downstream signaling cascade through the PI3 kinase-Akt pathway. This is a single-arm phase two study, where all patients receive Zenocutuzumab at the dose of 750 milligrams intravenously every other week. It includes patients with NRG1 fusion-positive cancers, and the primary endpoint is response rate. While the study is ongoing, based on early results, Zenocutuzumab has received FDA fast track designation. The third molecule being studied in this setting is Seribantumab. Seribantumab is an IgG2, monoclonal anti-HER3 antibody that blocks NRG1 from engaging its receptor; HER3. This is being studied in the CRESTONE study. This single-arm phase two study delivers Seribantumab intravenously weekly, and includes all NRG1 fusion-positive cancers. The primary endpoint is response rate, and early results were presented at ASCO 2022, but based on early signs of efficacy, Seribantumab was also granted FDA fast track designation.

If a patient has an NRG1 fusion-positive cancer, I think it is paramount to seek input about an NRG1 trial as soon as possible.

Even if the current therapy is working well, this allows other options to be kept open. It will be important to review inclusion criteria to help plan treatment strategies, and to understand the schedules and time commitment involved with each trial. In addition, it's important as much as possible, for oncologists and patients alike, to keep abreast of study and landscape updates. The greatest barrier to participating in an NRG1 trial is detection of the NRG1 fusion. Once however the fusion is confirmed, there are several tools that can help with trial involvement. Trials are updated regularly on Clinicaltrials.gov. They are not however updated immediately. Clinicaltrials.gov provides contact information for a person at each clinical trial site. These sites are scattered geographically to increase the likelihood of having a treatment center near every patient. I would encourage interested parties to contact their nearest investigator site, to seek advice on participation in these trials when appropriate.

It is important to note the schedule of treatment, and the need to travel in order to comply with the trial requirements. Note that costs are sometimes defrayed, and there are different programs that can help facilitate travel if that is the main barrier to participation. My number one tip is to not be afraid to ask for help. To reach out to other experts or the clinical trial sites to see how these treatments can be made available to patients with NRG1 fusion-positive cancers. Thank you for your attention.

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