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What Are NRG1 Gene Fusions and the Rationale for Targeting ERBB?

Announcer:
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Dr. Liu:
Hello. My name is Dr. Stephen Liu. I'm the director of thoracic oncology from Georgetown university in Washington, DC. This presentation discusses the questions What are NRG1 gene fusions? And what is the rationale for targeting ErbB? Unlike most therapeutic targets in oncology NRG1, or Neuregulin 1, does not refer to a trans membrane receptor kinase. Uniquely NRG1 is a ligand. This molecule contains an EGF-like domain. This domain serves as a ligand for the receptor HER3 or ErbB3. When NRG1 engages HER3, it prompts heterodimerization. The favored partner of dimerization is HER2. And so when NRG1 physiologically engages its receptor HER3, this heterodimerize to HER2. And this complex then triggers familiar downstream signaling cascades, including the important PR3 kinase AKT pathway, responsible for cell proliferation and survival.

Pathologic NRG1 fusions come in many different forms, but nearly all of these will retain the EGF-like domain of NRG1. This means the resultant product is still able to bind and engage HER3. The NRG1 fusion partner often provides a trans membrane domain. This essentially tethers the NRG1 ligand in close proximity to the HER3 receptor. This allows for prolonged exposure and abnormally increased signaling through the NRG1, HER3, HER2 pathway. Because of these binding partners, HER3 and its partner HER2, are thus rational therapeutic targets. In fact, there have been multiple early reports that have shown efficacy with targeting HER2 and/or HER3 in cancers that harbor a pathologic NRG1 fusion. Pan-ErbB kinase inhibitors like Afatinib have targeted that intracellular kinase domain and been effective. HER3 monoclonal antibodies like Seribantumab and HER2 HER3 by specific antibodies like Zenocutuzumab have all shown early efficacy in tumors with this rare, but important, genomic event. NRG1 fusions are very difficult to identify in large part because NRG1 is a very large gene. This gene alone constitutes 1/2000th of the entire human genome and nearly all of this over 99% is intronic or non-coding. What that means is DNA based detection strategies, or DNA based next generation sequencing, will have very poor or no coverage for NRG1. To detect NRG1 fusions consistently, one needs RNA-based next generation sequencing. In a retrospective analysis of specimens tested at Caris Life Sciences that we led from 2015 to 2019, we looked at all tumors that underwent RNA sequencing. And what we saw was NRG1 fusions are very rare events overall.

They were seen in only 0.2% of cases but they were seen across multiple tumor types. There was some enrichment for invasive mucinous lung adenocarcinoma and KRASS wild type pancreatic cancer but we found NRG1 fusions in biliary cancers, sarcomas, ovarian cancer, colorectal cancer and breast cancer. To summarize NRG1 fusions are rare, but now actionable driver events. These fusions lead to abnormal signaling primarily through the ErbB pathway. NRG1 serves as the ligand for HER3 that heterodimerizes to HER2 and triggers a familiar signaling cascade for which we have many interventions that can effectively block that signaling pathway. Detection of NRG1 fusions requires RNA sequencing and now multiple agents have shown efficacy and are under active investigation as potential therapeutic answers for these very rare but important events. Thank you for your attention.

Announcer:

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