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What Are the Clinicopathologic Features of NRG1 Fusion Tumors?

Announcer:
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Dr. Liu:
Hello. My name is Dr. Steven Liu. I'm the Director of Thoracic Oncology at Georgetown University in Washington, DC. This presentation is on the clinical pathologic features of NRG1 fusion tumors. NRG1 fusions are rare events. In an early analysis we sought to characterize these fusions by performing a retrospective study of specimens tested at Caris life sciences from 2015 to 2019. We looked only at tumors that underwent RNA sequencing with ArcherDX or whole transcriptome sequencing, because we know that RNA sequencing is really necessary to detect NRG1 fusions. What we found is that NRG1 fusions are seen across multiple cancer types but at the very low incidents.

Overall we detected 41 cases with NRG1 fusions out of over 21,000 cases sampled. That's an incidence of about 0.2%. There is some enrichment for NRG1 fusion in invasive mucinous adenocarcinoma of the lung and in K-ras wild-type pancreatic cancer. But in this study we found NRG1 fusions in gallbladder cancer, renal cell carcinoma, ovarian breast sarcoma, bladder and colorectal cancer. The NRG1 fusions we detected were very heterogeneous. Multiple different fusion partners were identified. In fact, over two dozen were characterized at the time of this initial analysis. Others have since been described. It is not clear what significance the fusion partner has. There were also many different co mutations present within these NRG1 fusion positive cancers. The co mutational landscape also is of unclear significance. And we do not know if this impacts the biology, the prognosis, or more importantly, the treatment of NRG1 fusion positive tumors. We saught to obtain more clinical information from NRG1 cancers. And so in collaboration with Drs. Alex Drilon, Michael Derousseau and Jacque Caudrenel, we launched the NRG1 registry.

This was a global registry for patients with non small cell lung cancer that harbored an NRG1 fusion. And through this global collaboration we identified over a hundred cases with clinical outcomes publishing these results in JCO 2021. What we found mirrored the heterogeneity seen in the initial analysis. There were many different fusion partners. The most common was CD74 seen in over 40% of cases in non small cell lung cancer. The second most common was SLC3A2 and there were interesting patterns. For example, ATP1B1 was a relatively rare fusion partner in lung cancer but we know it to be a more common fusion partner in pancreatic cancer. The significance of these differences is unclear. We looked at patterns of spread and as one would expect most patients had involvement of the lung and lymph nodes. Also common were bone and brain. Brain metastases identified in over 20% of patients with NRG1 fusion positive lung cancer. When we looked at the demographics of patients identified we found that more patients were female than male about a 60 to 40 split. The vast majority were never smokers.

Nearly 60% of patients with NRG1 fusion positive lung cancer had never smoked. There were variable stages of diagnosis with 32% presenting with early stage one disease and 29 presenting with stage four disease. But nearly all cases were adenocarcinoma, 94% including 57% invasive mucinous adenocarcinoma. What surprised us was how poorly patients did with standard therapy. The aggressive combination of chemotherapy and immunotherapy yielded a response rate of 0%, chemotherapy alone yielded a response

rate of only 13%. To summarize NRG1 fusions are seen across different tumor types but there is an enrichment in invasive mucinous non-small cell lung cancer and K-ras wild-type pancreatic cancer.

But it is important to keep in mind that NRG1 fusions are tumor agnostic seen in many different types of cancers. These are very heterogeneous events and a reminder that RNA sequencing is needed to identify them. In non-small cell lung cancer there's a large number of fusion partners and most patients with NRG1 fusion positive lung cancer were never smokers. With standard treatment, including combined chemo-immunotherapy, the outcomes are quite poor and seeking participation in a clinical trial with a novel NRG1 targeted agent is certainly an appealing option. Thank you for your attention.

Announcer:
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