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

HER2 & PD-L1: Exploring Clinical Characteristics of G/GEJ Cancers in Relation to Biomarker Positivity

Announcer:
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Dr. Janjigian:
Hello, my name is Dr. Yelena Janjigian. I'm a Medical Oncologist and Chief of GI Oncology Service at Memorial Sloan Kettering Cancer Center in New York. And we will discuss the clinical characteristics of gastric and gastroesophageal junction adenocarcinoma in relation to biomarker positivity, specifically pertaining to HER2 and PD-L1 overexpression, which are our standard biomarkers in our disease.

So, by way of background, in gastroesophageal adenocarcinoma, which is the most common subset of tumors that we see in the western population, overwhelming majority, 70% of these cases are chromosomally unstable, meaning they're characterized by aneuploidy p53 mutations and amplifications in genes such as HER2, VEGFR2, other RTK-driven genes. Of chromosomally unstable tumors, 30% are HER2 amplified and also have HER2 protein overexpression. And the other subset of tumors that are important in our disease is genomically stable tumors, which is 20%, and certainly microsatellite unstable and EBV positive tumors which represent 5% each. So, the bulk majority are chromosomally unstable. And those are the tumors that we have to think about and target in the clinic.

What about HER2? Within those tumors, HER2 positivity occurs in a high percentage of patients; higher so because in the gastroesophageal junction tumors than in stomach cancer, and in GE junction it's 30% HER2 positive and in stomach gets 10 to 20%. HER2 tumors are more likely to be intestinal than diffuse subtype, and historically they're overcome – their characteristic without HER2-director therapy is that they have worse outcomes unless you target HER2.

Co-expression and heterogeneity are a big issue in our disease. Heterogeneity within each patient and within each tumor, but also within different sites of tumor metastasis within each patient. In gastroesophageal cancer, we know that a level of PD-L1 is highest in HER2-positive tumors. And also, we see overexpression of MET in EGFR, which can impact sensitivity to the disease and treatment response.

What about PD-L1? We think about PD-L1 as an immune-related biomarker. And in other diseases such as lung cancer, these tumors commonly overexpress PD-L1 in the tumor. In our GI tumors, most of the expression happens in the stroma. And looking at prospectively collected phase 3 data, up to 60% of tumors have very high PD-L1 overexpression. We use it as a definition of PD-L1 CPS 5 or greater, and patients – in 80% of patients, tumors have PD-L1 CPS 1 or greater. So, at least, that is an important cutoff for you to know. The staining usually occurs both in the tumor and the stroma, although the stromal staining is much more prevalent. And we have a summary of what's different between TPS and CPS shown here. What I want you to remember is this CPS positivity, the assessment takes about 20 to 30 minutes per sample and is relatively operator-dependent because they have to count – the pathologist has to count every cell in the sample and estimate the number of positive cells, and then divide it by the denominator.

What about MSI? So MSI/MMR deficiency can be assessed by immunohistochemistry, that PCR test or next generation sequencing that

looks at tumor mutational burden and the microsatellite instability. The quickest way to do it is through immunohistochemistry by MMR testing, and those are four different unstained slides that you will need. And up to 5% of stage IV cancers lose expression of mismatch repair protein tumors. It's less common in esophagus cancer than gastric cancer. And looking at earlier stage disease, the rate of MSI positivity may be slightly higher, but it's relatively rare in unselected patient population.

So, in summary, we reviewed all the biomarkers for this disease, including PD-L1, microsatellite instability, and HER2. Those are important biomarkers to test in all stage IV patients. And also now increasingly, we're testing more and more patients with early or locally advanced disease, because microsatellite instability in particular, may have a significant impact on chemotherapy resistance, and so you would not want to give perioperative therapy in an MSI high population. So, it's critical to continue tests for these biomarkers in this rare subset of patients with esophageal and gastric adenocarcinoma.

Thank you for your attention.

Announcer:
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