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Claudin18.2: An Emerging Biomarker and Its Significance as a Therapeutic Target in G/GEJ Cancers

Announcer:
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Dr. Klempner:
Hello, my name is Sam Klempner. I'm a GI Medical Oncologist at Mass General in Boston, and I'm here to discuss Claudin18.2, an emerging biomarker and its significance as a therapeutic target in gastric and GE junction cancers.

So, as we all know, biomarker testing is increasingly central to selecting therapies for our patients with advanced unresectable and metastatic gastric and GE junction. And this slide is really just a high-level landscape review of the types of testing and the biomarkers that are central to exploring all therapeutic options for our patients. Currently, mismatch repair, HER2, and PD-L1 are all standard of care. Today, we'll be talking about CLDN18.2, which is another immunohistochemical test to identify patients who may benefit from CLDN18.2-directed therapies such as zolbetuximab.

As a little bit of background, Claudin18.2 is a member of the large tight junction protein super family. This is a highly conserved protein across multiple species. And usually, one of the unique aspects is that the expression is normally restricted to differentiated gastric epithelium, so there's not a lot of normal tissue expression outside the stomach. Functionally, CLDN18.2 regulates paracellular permeability in sodium and hydrogen ion transport in the tight junction intercellular spaces. And interestingly enough, if you knock out CLDN18 gene, mice are likely to develop lung and gastric tumors. But if you knock out only the 18.2 isoform, there isn't a phenotype. Shown here in the upper left is the protein sequence, also where most of the Claudin18.2 therapies, including zolbetuximab, bind in the extracellular loop 1.

Really, this is all about location. So, in tumor genesis, CLAUDIN18.2, becomes expressed more readily in the tumor cell surface, as opposed to in the tight junctions where it's less exposed in the normal epithelium. And this sets up a scenario where it becomes available as a target for antibody and other base therapies.

Importantly, this is actually a pretty prevalent biomarker. If you look at about 4,500 patients screened, what you'll see on the right is that around 38% of all of our advanced gastric and GE junction adenocarcinoma patients will be CLDN-positive at the threshold used for the SPOTLIGHT and GLOW trials.

This really can be anyone with gastric cancer. The point of this slide is that, unlike mismatch repair defects which rarely overlap with HER2 amplifications and positivity, Claudin18.2 can actually overlap with any biomarker. So, this underscores the need for testing, because we will have patients who are HER2-negative and CLDN-positive and even HER2-positive and CLDN-positive, and across all PD-L1 strata. So, it just - really the point here is that we need to test all of our patients because you can't base clinical features on who's more or less likely to be positive for CLDN18.2.

The testing, as I mentioned briefly, is a protein test done immunohistochemically. As you can see here, this is a scoring system in the available data that used a 75% of tumor cell with moderate to intense staining, so 2+ or 3+ membranous pattern. And you can see for pathologists, this is a relatively straightforward interpretation. And we expect Claudin18.2 implementation to be done in multiple ways; will be either brought on at our own institutions, could be sent out to third-party vendors or pathology suppliers, and there are also several antibody clones which have been compared to the 43-14A clone which was used in the zolbetuximab trials.

So, the key takeaways when you go to the clinic tomorrow is that this really is a new biomarker in gastroesophageal cancers. It's linked to benefit from zolbetuximab in two parallel phase 3 trials. It's highly prevalent, so almost a third of all of our patients are positive for CLDN18.2 at the cut-points established in the zolbetuximab data. This occurs across all biomarker subgroups, so PD-L1 high, PD-L1 low, HER2-positive, HER2-negative, etcetera, again, underscoring the need for testing. And this is an IHC test, so it's a relatively straightforward test to interpret, to identify our patients who may benefit from therapy.

Thank you very much for your time and I hope this was informative.

Announcer:
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