Transcript Details
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Advancing HER2-Targeted Therapy in GI Cancers

Announcer:
You're listening to *Project Oncology* on ReachMD. On this episode, Dr. John Strickler will share insights on the current state of HER2-targeted therapies for gastroesophageal cancer, which he spoke about at the 2026 ASCO Gastrointestinal Cancers Symposium. Dr. Strickler is a Professor of Medicine in the Division of Medical Oncology at Duke University School of Medicine and Co-Leader for the Precision Cancer Medicine and Investigational Therapeutics Program at the Duke Cancer Institute. Let's hear from him now.

Dr. Strickler:
HER2 has been an actionable target for upper GI cancer for several years now. We learned in 2010 from the ToGA trial that the addition of trastuzumab to standard chemotherapy provided significant survival benefit, so that became a standard of care. Then, we went through approximately a decade of negative trials where additional therapies were tried, and we attempted to improve upon that benefit from trastuzumab. Most of those trials were negative, so we were unsuccessful in moving the needle beyond trastuzumab.

All of that changed in 2020. Right around that timeframe, it became clear that the addition of pembrolizumab immunotherapy to trastuzumab provided substantial benefit, and then that was later amended to limit that immunotherapy to those patients with PD-L1-positive disease. So, we've seen that constant evolution towards more immunotherapy strategies. What we have now is a new study finally improving upon that standard of trastuzumab-based treatment, which found that zanidatamab is superior to trastuzumab. So that will become a new standard-of-care option in combination with chemotherapy, with or without immunotherapy.

Biomarkers play a very important role in the management of gastroesophageal cancer in particular. We knew in 2010 that HER2 is actionable, and that led to the approval of trastuzumab for those patients with HER2 positive disease, which meant that we needed to test our patients for HER2 overexpression by IHC with FISH if it was the intermediate expressing tumor. Added on top of that over the years, we have other important biomarkers. Mismatch repair from immunohistochemistry can predict significant benefit from immune therapies. Additionally, we have PD-L1; it's the CPS score that we use to predict benefit from immune therapies as well. And, more recently, we have Claudin 18.2, which is another immunohistochemistry marker that is used to predict benefit from zolbetuximab.

In addition to that, there are some other rare biomarkers that can be detected from genomic tests—what we call next-generation sequencing panels—to look for other targets of interest where there may be a pan-tumor approval. That could be, for example, NTRK fusions, which may predict benefit from an anti-NTRK therapy. And then there are some other pan-tumor approvals that could impact gastroesophageal cancer.

In addition to the established targets, we're increasingly looking for new ways to target KRAS. Occasionally, we will see KRAS mutations in patients with upper GI cancer, so that could potentially be actionable one day. But there are a number of other targets in development and therapies in development that may rely upon those tests.

For patients who have HER2-positive disease who progress on first-line anti-HER2-based therapy, we now have an FDA approved therapy in the clinic that's specifically designed to attack those cancers that become resistant. The name of that therapy is trastuzumab deruxtecan. It's an antibody-drug conjugate. It is an antibody, much like trastuzumab, but this one is linked up to a potent cytotoxic payload—a topoisomerase I inhibitor payload. So that antibody delivers a potent payload to the cancer and delivers significant benefit over standard-of-care chemotherapy.

We've had this approved for years, but recently, we have results from a large randomized trial finding that this antibody-drug conjugate, trastuzumab deruxtecan, is superior to the best second-line therapy we have to offer, and that would be chemotherapy plus ramucirumab. So, for those patients who are HER2 positive who progress on first-line therapy, that antibody-drug conjugate is the

standard of care and is FDA approved.

We now have a bispecific antibody, zanidatamab, which is already FDA approved for patients with HER2-positive biliary tract cancer—that's IHC 3+. And now, this drug has been tested head-to-head against trastuzumab in the first-line setting for HER2-positive gastroesophageal cancer, and zanidatamab appears to be superior to trastuzumab head-to-head.

Announcer:
That was Dr. John Strickler discussing the current state of HER2-targeted therapies for gastroesophageal cancer. To access this and other episodes in our series, visit *Project Oncology* on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening!