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Guideline Recommendations in First-Line Treatment of HER2-Negative Upper GI Cancers

Announcer:
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Dr. Cleary:
This is CE on ReachMD, and I'm Dr. James Cleary. The NCCN guidelines for gastric cancer and esophageal and GE junction cancers recommend various first-line therapies for patients with HER2-negative gastroesophageal cancer, and the treatment selections guided by biomarker testing. We're going to be talking about these different regimens today.

For tumors that are PD-L1 positive—and what I mean by that is tumors that have a PD-L1 CPS score 1 or higher—there are three different regimens. Each of these regimens are combined with chemotherapy, 5-FU and platinum-based chemotherapy, and an anti-PD-1 antibody.

The three different regimens are pembrolizumab with 5-FU and platinum chemotherapy, nivolumab with 5-FU and platinum chemotherapy, and tislelizumab with 5-FU and platinum chemotherapy.

The trials for pembrolizumab and nivolumab included as the chemotherapy regimens both FOLFOX, CAPOX and cisplatin 5-FU, whereas the trials for tislelizumab included CAPOX and FOLFOX. But really, when I think about this, if you have a PD-L1 positive tumor and you want to use an anti-PD-1 antibody, typically what I do, just because of tolerance, I give FOLFOX with the PD-1 antibody.

Recently, in addition to the checkpoint inhibitor regimens, the FDA has also approved a regimen for tumors that are claudin 18.2 positive. These regimens combine a claudin 18.2 antibody, zolbetuximab, with either FOLFOX or XELOX.

Putting this all together—and the way we use it in clinic—for tumors that are claudin 18.2 negative but PD-L1 positive, my practice is to use FOLFOX with a PD-1 antibody, either nivolumab, pembrolizumab, or tislelizumab. Similarly, for tumors that are PD-L1 negative but are claudin 18.2 positive, my practice is to use FOLFOX with zolbetuximab.

Obviously, the challenging part here, and where we don't have data to guide us is when you have a dual-positive tumor, when you have a cancer that's PD-L1 positive and claudin 18.2 positive.

I'll tell you the approach I have. Future clinical trials are going to sort of clarify this issue, but this is how I do it. If the tumor, in addition to being claudin 18.2 positive, has a PD-L1 CPS score of 5 or greater, I use FOLFOX with the anti-PD-1 antibody. The reason for that is when I talk to patients, they want therapies that are going to have a lot of durability. And I really think when you're talking about extreme outliers, really, what we will see, those patients with a lot of durability, it's usually from an anti-PD-1 antibody, such as nivolumab,

pembrolizumab, or tislelizumab. So again, if I have a tumor that's claudin 18.2 positive but has a PD-L1 score 5 or higher, I'm going to use FOLFOX and a PD-1 antibody, either nivolumab, pembrolizumab, or tislelizumab.

If it's, again, claudin 18.2 positive but the PD-L1 score is between 1 and 5%, that's even much harder. In those cases, I just sit down and talk to the patients. Some patients would prefer the claudin 18.2 antibody just because the results on the clinical trial look good, whereas others, again, just because of the chance of having long-term responses, would want to be on a PD-1 antibody. That situation, claudin 18.2 positive and PD-L1 score 1 to 5, is probably the hardest situation. Again, I just talk it through with my patients.

So PD-L1 CPS testing should be conducted to guide first-line treatment with immunotherapy. And really, for all patients with newly diagnosed metastatic gastroesophageal cancer, you should be ordering HER2 immunohistochemistry, mismatch repair immunohistochemistry, PD-L1 immunohistochemistry, and now claudin 18.2 immunohistochemistry.

The difficulty in getting claudin 18.2 positivity, depending on your institution, at my institution it’s not hard because it’s a routine test that the pathologists do for us. However, I could imagine that in the community, it is difficult, and that you have to send it to a central lab for immunohistochemistry.

Thank you.

Announcer:
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