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Emerging Directions in Biomarker-Directed Therapy for GI Malignancies

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Dr. Venook:
Hello. I'm Dr. Alan Venook. Our discussion today will focus on emerging data from trials evaluating biomarker-directed therapy that may impact current practice guidelines. And this will be an emphasis on upper GI malignancies, first and foremost, and the new target. The target is claudin 18 isoform 2.

Claudin 18 isoform 2 is a tight junction protein that is believed to be exposed to circulating cells or circulating immune cells at the time of malignant transformation. It's ubiquitous throughout the GI tract, especially rich in the upper GI system. The drug targeting this is an IgG1 antibody called zolbetuximab, which mediates its effect via antibody-dependent cellular cytotoxicity. So an immune-based therapy, part of in this particular tight junction protein expressed on cells.

Now, patients eligible for the studies I'll report and patients who could potentially benefit from this therapy are those that have positive staining for claudin 18.2. And the definition of positive staining, as any of you know who take care of these patients and wonder about how you decide if a patient is HER2-positive or negative, well, for claudin 18.2-positive patients, it requires that at least 75% of the tumor cells have moderate staining by immunohistochemistry. Of the broad population of patients considered for these studies that I'll discuss in a moment, about 40% of them who were screened met the criterion for claudin expression, so a common marker seen in many patients with an antibody targeting the marker. And the two studies I'm going to talk about are studies that are called SPOTLIGHT and GLOW. They're really the same studies. They were launched more or less at the same time.

SPOTLIGHT is the use of the antibody zolbetuximab in combination with FOLFOX chemotherapy. And GLOW is the same design study in patients with upper GI cancers, GE junction, or gastric cancer. And GLOW combined zolbetuximab with CAPOX, capecitabine and oxaliplatin. So oxaliplatin-based chemotherapy with the fluoropyrimidine with or without zolbetuximab.

The take-home message: Each of these studies showed a survival benefit approved to patients treated with the zolbetuximab who had the expression of the marker for claudin 18.2. And the difference was quite significant in terms of the number of months, favoring the zolbetuximab arm. Now, it is worth commenting and worth realizing that, in fact, the patients who had the FOLFOX did better than patients with CAPOX, although we have to dig into the data to understand if there's really a difference in the chemotherapy or perhaps a difference in the population of patients. One of the studies was more European-centric and one was Asian-centric. But the claudin 18.2 is a new target and, at least in the upper GI malignancies, seems to be a major advance. FDA approved this zolbetuximab in combination with a fluoropyrimidine-based chemotherapy.

Another area to talk briefly about in GI malignancies is a combination of trastuzumab and deruxtecan. This targets HER2-positive cancers. Obviously, HER2 is a valuable target in gastric and upper GI cancers, as well as in colorectal and other cancers and, of

course, in breast cancer, where trastuzumab first became popularized and was shown to be effective.

Trastuzumab/deruxtecan is an antibody-drug conjugate where the payload, the deruxtecan, the chemotherapy drug, is added to the humanized anti-HER2 antibody and essentially is targeted delivery to cancer cells. We've seen this quite effective in breast cancer, in bladder cancer with a variety of different antibodies and payloads or chemotherapies.

Trastuzumab deruxtecan has been studied in a series of studies called the DESTINY studies. They looked at a broad range of cancers, in particular, for example, in colorectal cancer, in HER2-expressing colon cancer patients. That's a minority of patients with colorectal cancer, but certainly they exist. And patients who are HER2 positive based on immunohistochemistry or FISH, with these patients, remarkably, many of them have major responses to the combination of trastuzumab deruxtecan, even though they'd failed a variety of other therapies, including irinotecan, which is a drug similar to deruxtecan.

So the targeted delivery of this chemotherapy via the antibody-drug conjugate has been shown to be quite effective. Again, a very promising therapy in a number of areas. And this, in particular, in colorectal cancer, we're quite excited about this.

Now, one thing to be aware of, this particular construct, this antibody-drug conjugate has a major toxicity of interstitial lung disease, pneumonitis, so be aware of that. And you have to watch your patients carefully. There have been a number of deaths from interstitial lung disease in the early studies with this drug. This is one of those drugs that might be better used earlier in treatment because it may be that the lung toxicity is a function of too much prior treatment before getting this antibody-drug conjugate.

But a very exciting development, these antibody-drug conjugates. And many more are on the horizon.

Thank you.

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