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Selecting First-Line Therapy in Gastric Cancers: A Biomarker-Driven Approach

Announcer:
You're listening to *Project Oncology* on ReachMD, and this episode is sponsored by BeOne Medicines. Here's your host, Dr. Jennifer Caudle.

Dr. Caudle:
This is *Project Oncology* on ReachMD, and I'm your host, Dr. Jennifer Caudle. Joining me to discuss how we can select a first-line therapy for gastric and gastroesophageal junction cancer based on biomarkers and other factors are Dr. Samuel Klempner and Dr. Nataliya Uboha. Dr. Klempner is an Associate Professor of Medicine at Harvard Medical School and a member of the Gastrointestinal Cancer Group at Massachusetts General Hospital. Dr. Klempner, welcome to the program.

Dr. Klempner:
Yes, thanks for having me.

Dr. Caudle:
And Dr. Uboha is an Associate Professor in the Division of Hematology and Oncology in the Department of Medicine at the University of Wisconsin, where she's also the Associate Director of Clinical Research at the Carbone Cancer Center. Dr. Uboha, it's great to have you with us as well.

Dr. Uboha:
It's a pleasure to be here.

Dr. Caudle:
Now, for some background, testing for biomarkers like PD-L1, HER2, claudin 18.2, and FGFR2b is really shaping how we approach first-line therapy in gastric cancer. So let's take an in-depth look at each one.

Starting with PD-L1, the CheckMate 649 study showed a survival benefit with nivolumab plus chemotherapy in patients with a CPS of 5 or greater, and pembrolizumab is another approved option for this group. So with all this being said, Dr. Klempner, what are your thoughts on the role of immunotherapy in the first-line treatment of PD-L1 positive patients? And how do you typically assess the risk-benefit balance for these regimens?

Dr. Klempner:
PD-L1 has emerged as one of the most important biomarkers for us to understand in our patients. So when newly diagnosed patients present to us—particularly we're talking about advanced disease in these trials—we try to understand what we can about the tumor to guide our choice in balancing efficacy and toxicity.

Dating back all the way to KEYNOTE-028, 059, and 062, we started to see that there was an association between immune checkpoint inhibitor outcomes and PD-L1 expression levels, and varying cut points have been used in multiple clinical trials. You mentioned CheckMate 649 and KEYNOTE-859, and there are now more than six phase 3 trials testing chemo with or without immune checkpoint agents in frontline gastric and esophageal cancers.

And when you pool the data, you start to see recurrent patterns. Largely, in patients who have no PD-L1 expression, whether it's by TAP or CPS scoring systems, it's really hard to show any benefit from the addition of immune checkpoint inhibitors. So as you alluded to, if there's not a clear benefit but there's a known toxicity profile, many of us—and this is consistent with the FDA labeling—will not give

checkpoint inhibitors to patients who have completely PD-L1 negative tumors. The greater than 1 is a very big group, and there are multiple cut points within that. There is greater than 1, greater than 5, and greater than 10, and there is somewhat of a linear relationship between degree of expression and magnitude of benefit.

Dr. Caudle:
And turning to you now, Dr. Uboha, let's move on to HER2. The FDA recently granted full approval to the KEYNOTE-811 regimen combining pembrolizumab, trastuzumab, and chemotherapy in patients who also express PD-L1. So how do you see this combination influencing HER2-positive treatment approaches, especially when it comes to balancing efficacy and tolerability?

Dr. Uboha:
So KEYNOTE-811 was a practice-changing trial. It was a phase 3 trial that looked at the addition of pembrolizumab to standard chemotherapy plus trastuzumab. We have used HER2-directed therapy for patients with HER2-positive gastroesophageal junction and gastric cancer for many years. The addition of pembrolizumab resulted early on in improved response rates, and ultimately, we saw that addition of pembrolizumab to what I call the ToGA regimen—or chemotherapy plus trastuzumab—ultimately demonstrated an improved overall survival.

We have seen the benefits primarily in patients who have PD-L1 positive tumors. As Dr. Klempner alluded to, that cutoff that we are seeing now across HER2-positive and HER2-negative disease is PD-L1 score of combined positive score 1 percent or greater. The good news for our patients is that there is significant overlap between HER2 expression and PD-L1 positivity, so over 80 percent or maybe even over 85 percent of patients would qualify for the addition of pembrolizumab to chemotherapy and trastuzumab.

Dr. Caudle:
Next is claudin 18.2. This is now an FDA-approved target in HER2-negative disease, with zolbetuximab plus chemotherapy showing significant overall survival and progression-free survival benefits in the SPOTLIGHT and GLOW trials. So sticking with you for just another moment, Dr. Uboha, what are the key safety considerations we should keep in mind when using this approach?

Dr. Uboha:
In normal tissue, Claudin is expressed in the lining of the stomach, and so some of the toxicities come from the off-target effect of anti-claudin agents. And so what we are seeing with anti-claudin antibody is primarily gastrointestinal toxicities, specifically nausea, vomiting, and gastritis. And this is something to keep in mind when we offer these drugs to our patients.

Dr. Caudle:
So coming back to you, Dr. Klempner, FGFR2b is emerging as a potential biomarker, especially following early data from the FIGHT trial that showed promise with bemarituzumab. And while it’s not yet FDA approved, where do you think FGFR2b testing might fit into the biomarker landscape, particularly for HER2-negative and PD-L1-low patients?

Dr. Klempner:
FGFR2 amplifications and fusions have been looked at pan-cancer, and FGFR2b is overexpressed at the protein level, depending on the cutoff you use in gastric and GE junction cancers—somewhere between 15 and 25 percent. And so based on this and the ability to develop antibodies against this surface marker, there was several trials launched. There was an initial phase 1 with bemarituzumab monotherapy, which showed that this drug as a single agent did induce some responses in pretreated patients with FGFR2b expression particularly.

And then they launched a randomized trial called FIGHT, as you mentioned, which basically compared chemotherapy against chemotherapy plus bemarituzumab in FGFR2b-positive patients. And we learned a bunch from that trial. One thing is that the cut point matters. It seems that patients in that trial in the upper level of expression—so more than 10 percent of tumor cells staining positive—had the greatest outcomes and greatest difference between chemotherapy. So that has been taken forward into two phase 3 trials. One is chemotherapy versus chemotherapy plus bemarituzumab or placebo, and the other one is chemotherapy plus immunotherapy plus bemarituzumab or placebo. So the FORTITUDE-101 and -102 trials have been eagerly awaited for in the field because they may introduce a new biomarker if positive.

I think we will see some data soon about how this plays out, and we've seen some press releases from the trial sponsor that may raise some questions about the data. And so we all just need to see the data to understand if and how we’re going to implement this testing. But if so, then it will become a test that we're obligated to understand for our patients so that we can have the whole set of biomarker data to inform the discussion, and it will become another thing that we need to all learn how to do for our patients.

Dr. Caudle:
Very well said. For those of you who are just tuning in, you're listening to *Project Oncology* on ReachMD. I'm your host, Dr. Jennifer

Caudle, and I'm speaking with Dr. Samuel Klempner and Dr. Nataliya Uboha about biomarker-driven strategies for first-line gastric cancer care.

So now that we've discussed these key biomarkers, let's examine some other factors that can influence our treatment decisions. Dr. Uboha, when multiple biomarkers are positive—let's say, PD-L1 and claudin 18.2—how do you decide which treatment pathway to prioritize?

Dr. Uboha:
This is a great question and probably one of the most common questions we get asked after the approval of zolbetuximab. In the trial that looked at the activity of zolbetuximab, immunotherapy was not included, and it was appropriate for the time when the trial was launched. But since then, we have three anti-PD-1 agents approved for the treatment of this disease in the first line, as Dr. Klempner alluded to—tislelizumab, nivolumab, and pembrolizumab—and most patients do have expression of PD-L1. And so it is not infrequent, actually, in clinical practice that we see patients who have concurrent expression of several of these biomarkers, and so we have to make a decision, as you alluded to.

We have to take into consideration both efficacy and safety. I want to point out that the addition of immunotherapy resulted in improved overall response rate in addition to overall survival, while the addition of zolbetuximab did not improve response rate. So in our patients, frequently, we do need to see responses because they come and see us with a lot of symptoms related to their tumor.

The other thing that Dr. Klempner alluded to is that we actually see better responses to immunotherapy with higher PD-L1 scores. It's not a perfect correlation, but that correlation does exist across studies. So of course, if a patient has a higher PD-L1 score, we would be more tempted to use immunotherapy. It is much tougher in patients who have lower PD-L1 scores and concurrent claudin expression.

But it is important to remember that there are some patients who will not be able to tolerate anti-claudin agents if they already have a lot of intractable nausea or gastritis; that might be a challenging drug to give. And there are also patients who have contraindications to immunotherapy or may have already received immunotherapy in the perioperative or adjuvant setting. In those patients, we would favor using zolbetuximab.

Dr. Caudle:
Great. Thank you. And before we close, I'll come back to you, Dr. Klempner, for the final question. What patient-specific factors do you typically consider when choosing between immunotherapy and targeted therapy options?

Dr. Klempner:
All of our drugs have some toxicity profile, and some are unique to a class of drugs as Dr. Uboha mentioned, like nausea and vomiting with zolbetuximab, immune-related adverse events with checkpoint inhibitors, and then very rare cardiotoxicities and things with HER2 drugs. So obviously, for patients who have preexisting conditions in one of those areas, we may have some concerns about giving that drug. If someone has a bowel obstruction and they have horrible nausea, it's hard to give a drug that makes nausea worse. If someone has a preexisting Crohn's disease and has needed to be on and off disease-modifying agents, we may have some pause about giving immune therapy drugs.

And so there's definitely patient-specific factors that influence our decision, and, of course, the most important one is the patient's input themselves. This is, as we say, shared decision-making. And so we present the pros and cons and the options and the expectations to the patients, and then we have a discussion.

But certainly, comorbidities that increase the risk of toxicity are things that we weigh heavily, and some are absolute contraindications. Somebody who requires 20 mg of prednisone a day to manage their refractory Crohn's disease is probably not someone we're going to ever give immunotherapy to, whether the patient really wants it or not. So I think there's a lot of need to understand our patients and their expectations and wishes to really individualize this. And then, of course, our population is also older, so the intensity of some of our chemotherapies also needs to be considered when discussing with older patients.

Dr. Caudle:
Wonderful. And with those key considerations in mind, I'd like to thank my guests, Dr. Samuel Klempner and Dr. Nataliya Uboha, for joining me to discuss first-line therapies for gastric and gastroesophageal junction cancer and how we can optimize our treatment selection. Dr. Klempner and Dr. Uboha, it was great having you both on the program.

Dr. Klempner:
Yes, thank you very much.

Dr. Uboha:
Thank you.

Announcer:
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