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Differentiating Biomarker-Driven First-Line Treatment Strategies in Metastatic Gastric/GEJ Cancers

Announcer:
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Chapter 1

Dr. Uboha:
This is a CME on ReachMD, and I'm Dr. Nataliya Uboha, associate professor at the University of Wisconsin. Today, we will be discussing biomarker-driven first-line treatment strategies in metastatic gastric and gastroesophageal [GE] junction cancers. So let's begin.

Let's start with talking about clinically relevant biomarkers in upper GI cancers. To start, we are talking about anatomically and molecularly heterogeneous diseases. There are several relevant biomarkers that are already incorporated in our current practice, and there are some that are under active investigation. The current biomarkers include microsatellite status, HER2 status, and PD-L1 expression status. And the biomarkers that are furthest along under investigation are claudin 18.2 and FGFR2b. Of note, microsatellite status should be determined regardless of stage, while the other biomarkers at present time are more relevant for patients with advanced disease.

So how do we test for microsatellite instability? There are several ways to determine whether tumors have microsatellite instability. The easiest is to look at the expression of mismatch repair proteins. This is an immunohistochemistry test. The turnaround for this test is 1 to 2 business days, and it is, in our practice, done as a reflex test for patients with all GI cancers regardless of stage. You could also look for microsatellite instability using PCR-based assays, and all next-generation sequencing [NGS] tests include testing for microsatellite instability as well.

So let's move to HER2. HER2 status should be assessed in all patients who have advanced gastroesophageal adenocarcinoma. In our institution, this is a reflex testing. Per NCCN Guidelines and per ASCO guidelines, HER2 testing in patients with gastroesophageal adenocarcinoma should be started with IHC testing, immunohistochemistry testing. Those that have 3+ tests, as indicated in this graph, are considered to be HER2 positive. Those that have no expression of HER2, so IHC 0, or have low expression of HER2, such as IHC 1+, are considered to be negative. And those patients whose tumors have HER2 IHC 2+ are considered to have equivocal HER2 expression, and subsequent FISH testing should be performed to determine whether the tumor has HER2 expression or not.

PD-L1 testing has also recently become part of the standard test for patients with advanced upper GI tumors. At present time, there's many different ways to look for PD-L1 expression. And currently, combined positive score, or CPS, is the most relevant test for patients with advanced gastroesophageal adenocarcinomas. Combined positive scores looks at the PD-L1 expression on tumor cells,

lymphocytes, and macrophages. Once we know the number of PD-L1-positive cells, this number is divided by the total number of viable tumor cells and multiplied by 100. And at least 100 viable tumor cells must be present for the pathologist to determine the combined positive score.

Another test that's entering our clinical practice is tumor area positivity [TAP]. It's somewhat similar to CPS and looks at the ratio of the area occupied by PD-L1-positive tumor cells and immune cells divided by total tumor area. There's no cell counting required, and it is a faster test to determine the score. TPS is less relevant for gastroesophageal adenocarcinoma because tumor cells do not express PD-L1 to a significant extent in these tumors. We are now learning that there is a significant concordance between different scoring methods, in particular CPS and TAP score, which is reassuring because it means we can at least compare and look at the results of different studies that utilize different scores.

An emerging biomarker for patients with this disease is claudin 18.2. We're not using it in standard practice yet, but we are anticipating that claudin-directed therapies will be approved in the near future, and we will talk about it during the later portion of this presentation. So claudin 18.2 is a tight junction protein. There are several different tight junction proteins, and claudin 18.2, in particular in normal cells, is expressed primarily in gastric mucosa. Claudin 18.2 has 2 extracellular loops, and one of those extracellular domains becomes accessible for antibody binding when cells undergo oncogenesis.

With the emergence of new biomarkers, there's going to be a question of biomarker overlap, and it will create a challenge in practice on how best to approach patients who don't have just one biomarker based on which we can select therapy but that have multiple biomarkers present within the same tumor. And so we already are collecting data as to what percentage of patients have both PD-L1 and claudin expression, which percentage of patients have both HER2 and claudin expression, or what patients have microsatellite unstable tumors and also have claudin expression. This data is emerging, and we are going to learn more and more about this overlap as we start testing more patients' tumors for claudin as well as HER2 and PD-L1 in clinical practice. But I anticipate that treatment selection will not only depend on the efficacy of treatment, but also on toxicity profile of each therapeutic agent, that turnaround time for testing results will also play a significant role on how we select treatments, and tissue availability will also become an issue. Since a lot of these biomarkers are immunohistochemistry based, we will need to make sure that there is enough of the tumor sample for us to be able to perform all of these tasks on patient samples.

I believe that sequential testing will be a challenge for our patients. In our institution, we are incorporating more and more of reflex testing. So as I've said earlier, all patients with advanced disease undergo reflex testing for PD-L1, CPS in my institution, for HER2 status, and also for microsatellite instability via MMR IHC. And so I think reflex testing for all the relevant biomarkers will be the right path forward to make sure that we can select the best treatment option for our patients in a timely manner.

We will now move on to talk about recent advances in the treatment selection for patients with advanced upper GI cancers. There are a growing number of new treatments that are biomarker based. As we talked about this earlier, the established biomarkers that have associated treatments are HER2, MSI, and PD-L1, and there are several emerging biomarkers as well.

Chapter 2

Dr. Uboha:
Let's start by talking about approaches to patients with HER2-negative gastroesophageal adenocarcinoma. In patients with HER2-negative gastroesophageal adenocarcinoma, immunotherapy plays a critical role when added to chemotherapy.

The addition of immunotherapy is based on several phase 3 studies. CheckMate 649 was a phase 3 global study that looked at the role of nivolumab in addition to chemotherapy versus chemotherapy alone in first-line setting for advanced gastroesophageal adenocarcinoma. There was also an immunotherapy-only arm, but we will not concentrate on that arm since it did not result in improved efficacy. So addition of nivolumab to chemotherapy resulted in improved overall survival in all randomized patients and in particular in patients whose tumors had PD-L1 CPS 5 or greater. With a longer follow-up time, and on this graph we have seen 36 months' follow-up, we have seen that the signal that was seen earlier is maintained. In fact, overall survival rate of 21% at 36 months is very encouraging since we have not seen these types of survival rates with standard chemotherapy in the past.

But I do want to bring up the subgroup analysis from CheckMate 649 to your attention. When we looked at overall survival based on PD-L1 score, patients who had tumors with PD-L1 CPS less than 5 or less than 1 really did not experience significant improvement with addition of nivolumab. In addition, response rate was not improved, but nivolumab was added to chemotherapy in patients whose tumors had PD-L1 CPS less than 5 or less than 1. And as such, even though nivolumab has broad approval by the FDA regardless of the PD-L1 expression, NCCN recommendations are more nuanced, and category 1 recommendation for nivolumab is restricted to patients whose tumors have PD-L1 CPS 5 or greater tumors. It is encouraging to see that there were no new or unexpected safety signals related to nivolumab. We saw expected immune-mediated toxicities, but there were no unexpected safety signals when

nivolumab was combined with chemotherapy and was generally well tolerated in this patient population.

KEYNOTE-859 was a similar study with pembrolizumab. The study also led to immunotherapy approval in first-line setting. In this phase 3 study, pembrolizumab was added to chemotherapy in first-line treatment for patients with advanced gastric and GE junction adenocarcinoma. Patients were randomized in a 1:1 fashion to either pembrolizumab or placebo plus chemotherapy. And again, it was a positive study in favor of pembrolizumab over placebo. Overall survival was improved with pembrolizumab addition. Overall response rate was improved. However, when we look at overall survival in prespecified subgroups, we see that patients with PD-L1 CPS less than 1 tumors did not experience significant improvement in overall survival. Again, similar to the CheckMate 649 study, there were no new safety signals.

And the other study that I would like to bring up is RATIONALE-305. Although tislelizumab, which is an anti-PD-1 antibody used in this study, has not received FDA approval yet in this setting, BeiGene submitted a license application to the FDA for review in this setting. RATIONALE-305 was a phase 3 study that looked at tislelizumab versus placebo with chemotherapy in patients with advanced gastric and GE junction adenocarcinoma. Again, very similar design to design of CheckMate 649 and KEYNOTE-859. The primary endpoint was overall survival in patients with PD-L1-positive tumors. Of note, PD-L1 positivity in this study was evaluated using TAP score, which is tumor area positivity score that we addressed earlier. So a bit different from CheckMate 649, but as we've discussed earlier, there's significant overlap between patients whose tumors have PD-L1 CPS-positive versus TAP-positive tumors. Similar to the other 2 studies, we are seeing an improvement in overall survival in patients with PD-L1 TAP 5 or greater tumors with the addition of tislelizumab. We're also seeing an improvement in overall response rate and progression-free survival. Again, there were no new safety signals, and we saw similar safety profile to other anti-PD-1 inhibitors when added to chemotherapy in this patient population.

So the key takeaways from that portion of this talk are that all advanced gastroesophageal adenocarcinomas should be tested for PD-L1 expression. Chemotherapy with anti-PD-1 agents is now standard first-line treatment for patients with PD-L1-positive tumors. Pembrolizumab and nivolumab are currently FDA-approved for this indication, and tislelizumab is under review at the FDA. We are seeing similar efficacy trends across anti-PD-1 agents with limited activity observed in patients that have low expression for PD-L1 in their tumors. And we also are not seeing any new concerning safety signals when anti-PD-1 agents are added to chemotherapy.

Chapter 3

Dr. Uboha:
So we will move on now to treatment of advanced HER2-positive upper GI cancers. To set the stage, about 15% to 20% of gastroesophageal adenocarcinoma are considered to be HER2 positive. We talked about HER2 testing earlier, and HER2 testing is indicated for locally advanced and inoperable, recurrent, or metastatic tumors. At this time, there are no data to support targeting HER2 in early-stage disease, but it is important to know that HER2 expression can change over time in advanced disease, and there are significant heterogeneity in HER2 expression even between metastatic sites. In addition, concurrent alteration and other signaling cascades and these changes in expression can affect therapeutic options and the benefits we see from treatments.

So let's start out with the case. This is a patient of mine who was 69 at the time of diagnosis. He presented with a 3-month history of progressive dysphasia. Endoscopy demonstrated partially obstructing malignant esophageal tumor at GE junction with extension to gastric cardia. And on pathology, we found invasive adenocarcinoma which was moderately differentiated. There was no loss of nuclear expression of mismatch repair proteins, PD-L1 CPS was 5%, and HER2 was IHC 3+. This patient had extensive liver involvement. You see the representative images from CT scans on the right-hand side. And he also had extensive retroperitoneal lymphadenopathy, all consistent with metastatic disease. So how do we approach this case?

Up until recently, we used to treat patients with this disease per ToGA regimen. So ToGA trial, the results of which were published now over 10 years ago, was a phase 3 trial that looked at the addition of trastuzumab to chemotherapy in first-line setting. Patients with advanced HER2-positive gastric cancer were randomized into 1:1 fashion to either chemo or chemo plus trastuzumab. And we saw an improvement in overall survival with trastuzumab addition, particularly in patients that had HER2 IHC 3+ tumors or HER2 IHC 2+ and FISH-positive tumors. This established trastuzumab as the standard treatment in first-line setting, in addition to chemotherapy, in patients with these biomarker-defined tumors. Since then, there have been several efforts to improve and to develop other HER2-directed therapies in upper GI cancers, in part following paradigms that we have seen in breast cancer. And unfortunately, many of those efforts were unsuccessful.

What we have learned from ToGA trial though, that biomarker selection matters. The improvement in overall survival in ITT [intention-to-treat] subjects looked much less pronounced than those that actually had higher HER2 expression. So we have seen already back then that the level of HER2 expression matters. And we have seen more recent publication that they have done further analysis on this issue and have demonstrated that patients whose tumors have higher level of HER2 expression or higher level of HER2 amplification

derive more benefit from targeting this pathway.

In addition, the presence of other alterations also matter. This is the work that was done by Dr. Janjigian and the team from Sloan Kettering that looked at the outcomes of patients with HER2-positive tumors depending on the presence of other alterations on NGS, such as alteration in RAS signaling. And certainly, those patients who had no other alterations, a yellow line on the Kaplan-Meier curve on the right-hand side, had better outcomes compared to those that had concurrent alterations in RAS pathway, a blue line. So those details also do matter in terms of expectations and what we can achieve from targeting HER2 pathway in this patient population.

The other important point is, and as to why some of the studies were negative in the past, is that HER2 expression can change over time. And so some of the second-line studies that did not provide positive results may have been because HER2 expression was not rechecked at the time of progression on trastuzumab. And we know now from prior studies that, according to some of the results, up to 30% of patients, as seen in T-ACT trial on the left-hand side, can lose HER2 expression after their tumors start to progress on trastuzumab therapy.

So ToGA has been a standard therapy for first-line setting, but recently, immunotherapy has also entered our treatment paradigm for patients with HER2-positive disease, similar to HER2-negative disease. And this is based on the results from KEYNOTE-811 study. KEYNOTE-811 was a large phase 3 study, an international study that enrolled patients with HER2-positive gastroesophageal adenocarcinoma. Patients were randomized into 1:1 fashion to either trastuzumab plus chemotherapy, the ToGA regimen, or trastuzumab plus chemotherapy plus pembrolizumab. The primary endpoint was overall survival and progression-free survival. KEYNOTE-811 had a preplanned interim analysis after enrollment of about 260 patients. During first interim analysis, overall response rate was evaluated, and we saw a significant improvement in overall response rate, 74.4% versus 51.9%, in patients who received pembrolizumab. So even though survival data was not available yet, pembrolizumab received accelerated FDA approval after these data were presented in 2021.

However, there were remaining questions about the results of the study, and the enrollment was still ongoing at that time. And one of the questions was, does PD-L1 expression matter? Since then, we have seen 2 other interim analyses. I will skip to the third interim analysis right now. And this third interim analysis was presented at the end of 2023 with a median follow-up time of 38.4 months. And what we have learned during that analysis and as well as second analysis as well, is that PD-L1 expression matters in these tumors as well. Notably, 85% of patients in KEYNOTE-811 had PD-L1 CPS 1 or greater tumors. However, the benefit of pembrolizumab was primarily seen in patients with PD-L1 CPS-positive tumors, and as such, FDA restricted pembrolizumab approval to those whose tumors have PD-L1 CPS 1% or greater, as well as HER2 positivity. We are seeing impressive overall survival with pembrolizumab addition, 20 months versus 16.8 months. Response rate, although a bit lower than during the first interim analysis, is still improved with pembrolizumab addition, and we have seen no unexpected new safety signal. Of note, we have learned now that as of May 2024, Merck announced that KEYNOTE-811 met dual primary endpoint overall survival, and we will see the final results of the study at the upcoming ESMO meeting in Barcelona.

So this is the kind of results you can see with this regimen. My patient had extensive liver involvement at the time of diagnosis, and after 6 months of FOLFOX, trastuzumab, and pembrolizumab, had significant downstaging of tumors. So responses are seen in clinic. Responses can be quite deep, and patients derive significant benefit from this combination, if chosen appropriately based on their biomarker positivity.

So my key takeaways from this portion of the presentation is that all advanced HER2+ gastroesophageal adenocarcinomas should be treated with trastuzumab-containing regimens in the first-line setting. In addition, pembrolizumab should be added to treatment if tumors also have PD-L1 CPS 1 or greater score. KEYNOTE-811 regimen produced significant response rate. These responses are clinically relevant. We also will see the final overall survival analysis at the upcoming meeting, and there were no unexpected safety signals with this regimen.

Chapter 4

Dr. Uboha:
So we'll move on now to talk about some of the novel biomarker-based therapies. Since we are talking about HER2-positive disease, let's start with zanidatamab. Zanidatamab is a bispecific HER2-directed antibody. It binds to 2 different HER2 epitopes. It binds to the same epitope that trastuzumab binds and it also binds to the pertuzumab-binding epitope. It has potent activation of ADCC and has shown single-agent activity across tumor types in late-line settings. This is an impressive waterfall plot for a single-agent antibody, including in patients who had prior HER2-directed therapies.

So we saw the results from the phase 2 study of zanidatamab plus chemotherapy in first-line HER2-positive gastroesophageal

adenocarcinoma. There was an impressive overall response rate, although small numbers, but you see a response rate of 75% in first-line setting. And based on these results, HERIZON-GEA-01, a phase 3 study of zanidatamab plus chemotherapy plus tislelizumab, was launched and is currently enrolling patients. The study will look at the addition of both zanidatamab and tislelizumab anti-PD-1 antibody in HER2-positive gastroesophageal adenocarcinoma.

The other agents that are entering our treatment paradigms are agents that are going after claudin. We talked about claudin 18.2 as an emerging biomarker earlier. There are many different ways to target claudin. And we've seen signals of activity with all of these strategies, including bispecific antibodies, monoclonal antibodies, antibody-drug conjugates, and even CAR T cells. Zolbetuximab is the furthest along in investigations. Zolbetuximab is an anti-claudin antibody that has been evaluated in two phase 3 studies, SPOTLIGHT and GLOW, that looked at the addition of zolbetuximab to first-line chemotherapy in patients with advanced gastroesophageal adenocarcinoma. In phase 3 SPOTLIGHT and GLOW studies, claudin positivity was defined as 75% of tumor cells showing moderate to strong membranous claudin 18 expression.

SPOTLIGHT and GLOW were two phase 3 studies that look at the addition of zolbetuximab to chemotherapy in a first-line treatment of locally advanced or metastatic gastric and GE junction adenocarcinoma. In the GLOW study, CAPOX chemotherapy was used as a backbone. And SPOTLIGHT, FOLFOX chemotherapy was used as a backbone. Both studies demonstrated improvement in overall survival. In SPOTLIGHT study, median overall survival was 18.23 months versus 15.54 months in experimental versus control group. And in the GLOW study, median overall survival is 14.39 versus 12.16 months in experimental versus control group.

It's important to note that overall response rate was not improved with the addition of zolbetuximab, which is a difference between targeting zolbetuximab and targeting anti-PD-1 in this patient population. But these were 2 positive studies that resulted in improved overall survival and progression-free survival, and as such, we anticipate approval of zolbetuximab for this indication in the near future. Neither the control arm nor the experimental arm included immunotherapy in their treatment regimen, and this is reflective of the time that this study was launched; neither nivolumab nor pembrolizumab were approved for gastroesophageal adenocarcinoma at the time of the enrollment to SPOTLIGHT or GLOW studies. However, our standard treatments have changed now, and certainly this question of biomarker overlap will become a very relevant issue as we start to incorporate zolbetuximab in our clinical practice going forward.

Because claudin is normally expressed in gastric mucosa, some of the adverse events that emerge from these studies are likely related to the on-target binding of claudin. We saw nausea and vomiting as significant side effects when zolbetuximab was added to chemotherapy. And this is something that will likely need to be addressed as we start to use this agent in standard of care practice.

The other novel agent that is currently in late-line studies, is bemarituzumab. Bemarituzumab is a first-in-class humanized IgG1 monoclonal antibody against FGFR2b. It has antitumor activity via blockade of FGFR2-dependent signaling and antibody-dependent cell-mediated cytotoxicity. And there are currently two phase 3 studies that are ongoing, and they are looking at the combination of FOLFOX and bemarituzumab or FOLFOX and nivolumab and bemarituzumab in the first-line setting. And these phase 3 studies were launched based on the efficacy of bemarituzumab observed in a phase 2 FIGHT trial. Addition of bemarituzumab to first-line chemotherapy resulted in promising overall survival improvement in biomarker-defined patient population, especially in those that had higher FGFR2b expression. There were some toxicities that were observed, including corneal events. Again, this will have to be taken into consideration as we select treatments of our patients, especially in those who have overlapping biomarker expression.

A couple of other biomarker-based therapies that are further behind. One of them is DKN-01. It's a humanized monoclonal antibody against DKK1. DKK1 modulates Wnt signaling and promotes proliferation, metastases, angiogenesis. It's also been shown to suppress antitumor immune responses, and it activates Akt signaling through the CKAP4 receptor. DKN-01 in combination with tislelizumab and chemotherapy in the first-line setting demonstrated significant response rates, although the study was quite small, but tumoral DKK1 mRNA expression is emerging as yet another biomarker, based on which we can hopefully start to choose treatments for our patients. Again, these are the results of the phase 2 studies, so certainly confirmatory phase 3 studies are needed. But there is a promising signal that was seen in the study.

Chapter 5

Dr. Uboha:
So let's move on to management of treatment-related toxicities. So we are utilizing immunotherapy in the management of patients with advanced gastroesophageal adenocarcinoma. Immune checkpoint inhibitors are associated with immune-mediated toxicities, and depending on that severity and organ affected, they can be managed differently. I tend to refer to NCCN Guidelines for the management of immunotherapy-related toxicity, as well as ASCO guidelines for the management of immunotherapy-related toxicities. As I've stated previously, the organ involved and the severity of the toxicity will dictate on how we approach patients with these side effects. For

example, patients who have asymptomatic thyroiditis and resultant hypothyroidism can frequently be continued on treatment without interruption but will likely require supplementation of their thyroid hormones with levothyroxine. On the other hand, patients who develop immune-mediated cardiac toxicities will likely require permanent discontinuation of immunotherapy agents because of significant risks associated with this type of toxicity.

We can also see immune-mediated toxicities that kind of fall in between these 2 prior examples. For example, patients who develop hepatitis or pneumonitis will require interruption of their treatment with immune checkpoint inhibitors and frequently will require steroids. However, those that have full recovery from these immune-mediated toxicities can sometimes be safely rechallenged in the future and can be re-treated with anti-PD-1 agents. And again, NCCN Guidelines is a great document to refer to for specifics on the immune-mediated toxicities that we can see in clinic.

In terms of other biomarker-based therapies in first-line setting, zolbetuximab, which we anticipate will be approved in the near future, has significant GI-associated toxicities, as I mentioned earlier. The most frequent treatment-related adverse events were nausea, vomiting, decreased appetite, as well as neutropenia, probably related to chemotherapy, in two phase 3 studies. As we talked about this earlier, GI toxicities, and nausea and vomiting in particular, are thought to be on-target effects of zolbetuximab, given normal expression of claudin 18.2 in gastric mucosa. And management strategies should include antiemetics, dose interruptions, and infusion rate adjustments as we start to use this drug in practice. Consensus guidance for management of nausea and vomiting in patients treated with zolbetuximab and chemotherapy are currently under development.

So in summary, gastroesophageal adenocarcinomas are a group of heterogeneous disorders. Personalized approaches are key for best patient outcomes. Reflex testing for mismatch repair protein expression, HER2, and PD-L1 combined positive score are current standard of care. Claudin 18.2 is an emerging biomarker, given expected approval of zolbetuximab in the first-line setting. And it is important to know that biomarker overlap will challenge our clinical decision-making in practice. And both safety and efficacy of treatments will need to be considered for best treatment selection for our patients.

Chapter 6

Dr. Uboha:
Good morning, everybody. Thank you for listening in and participating in this webcast. There are several questions coming in, the most important one being, I think, about zolbetuximab and how to incorporate this drug into our clinical practice. And just to bring everybody up to speed, zolbetuximab, an anti-claudin antibody, was just approved by the FDA. It was approved to be used in patients with advanced gastroesophageal adenocarcinoma in combination with first-line chemotherapy, the FOLFOX or CAPOX, in patients whose tumors express claudin. So at the time that I recorded my presentation, zolbetuximab was under the review by the FDA, but now we have an official approval. And so the question is, now that it's approved, how are you going to use it?

Certainly, biomarker testing is very important in patients who have claudin-positive tumors. Zolbetuximab should be offered in combination with chemotherapy. But the challenge is going to be: How do we pick the right treatment for patients who have dual biomarker positivity, such as both claudin-positive and PD-L1-positive tumors? I think in patients who have high expression of PD-L1, CPS 10 or greater, my preference would be to use anti-PD-1 agents.

One important distinction between the activity of zolbetuximab and nivolumab, for example, in this setting is that the addition of nivolumab improves overall response rate in these tumors. We see improved overall survival with the use of zolbetuximab in combination with chemotherapy, but unfortunately, addition of zolbetuximab to chemotherapy did not improve overall response rate in both SPOTLIGHT and GLOW trials.

In my practice, where I see a lot of patients with GE junction tumors who have a lot of disease-related symptoms such as dysphagia, inability to tolerate PO, response is important, especially early in the course of the treatment, because these responses actually would allow us to give further treatments to these patients. And so if I have patients who have high PD-L1, the decision is going to be quite simple: I will favor the use of immunotherapy. In those who have low, it will be trickier.

And there are already ongoing studies that are combining both anti-PD-1 and anti-claudin agents. But until that information is available regarding the utility of both anti-PD-1 and anti-claudin targeting in this disease, we will have to figure out how to use it. I suspect that earlier on, there will be a higher use of anti-PD-1 agents because of familiarity. But certainly if somebody has low PD-L1 score and high claudin expression, I would favor the use of zolbetuximab in those patients. For example, right now I have a patient in my practice, 90% of tumor cells have a moderate to high expression of claudin, and I'm certainly trying to get this patient on claudin-directed therapy on trial right now.

The other thing that can change our utilization of these drugs in the future is if one of the ongoing perioperative studies with immunotherapy turns out to be positive and if we start to incorporate immunotherapy in perioperative settings for those patients who have recurrences, we may consider switching a targeted drug to claudin targeting if the right biomarker is present.

The other question is: What is the optimal PD-L1 CPS cutoff to use a PD-1 antibody with chemotherapy in HER2-negative disease? Great question. FDA just had an ODAC [Oncologic Drugs Advisory Committee] advisory meeting in September, trying to really figure out what should be the right cutoff and how best to simplify the recommendations regarding the use of several anti-PD-1 agents in this disease. At this time, both nivolumab and pembrolizumab are approved for GE junction and gastric adenocarcinoma in combination with chemotherapy in first-line setting. I'm speaking specifically about HER2-negative tumors. Nivolumab is also approved with the chemotherapy in esophageal cancer. And pembrolizumab was studied in esophageal cancer in the study that enrolled both adenocarcinoma and squamous cell tumors.

And while FDA approved these agents regardless of biomarker status, we know from both of these studies that the activity is seen primarily in patients who have PD-L1-positive tumors. We use combined positive score to determine positivity of PD-L1 expression. And currently, the recommendations of the FDA or the FDA approval and ASCO and NCCN recommendations are not aligned, and there are different cutoffs that are used, 1, 5, or 10, depending on the drug that's utilized.

The other drug that we are anticipating approval, hopefully soon, is tislelizumab. It's another anti-PD-1 agent that was studied both in gastric and GE junction adenocarcinoma as well as esophageal tumor, squamous cell tumors, and have demonstrated similar efficacy when used in combination with chemotherapy. And just to confuse the issue further, tislelizumab studies utilized a different scoring system for PD-L1. They used TAP scoring system, tumor area positivity, with different cutoffs as well.

And so what we are learning now is that the good news is that CPS and TAP scores have significant amount of correlation and can be used almost interchangeably. So you basically, with TAP positive score and CPS, and CPS with a TAP cutoff of 1 or 5 and CPS cutoff 1 and 5, for example, you are identifying very similar patient population. And so you could almost interpret these results interchangeably.

What the FDA has done, they actually have done a great pooled analysis across all 3 studies with nivolumab, pembrolizumab, and tislelizumab. And across that pooled analysis, what they have seen, that patients with PD-L1 CPS less than 1 definitely do not respond from addition of immunotherapy. The strongest signal that we see is in PD-L1 CPS 10 or greater; 1 to 10 is a little bit more nuanced. My recommendation is to use PD-L1 CPS 1 or greater as a cutoff. I think in the patient population where treatment options are limited, given the difficulties with PD-L1 testing in practice, when I see patients in my clinic, I offer immunotherapy use to those with PD-L1 CPS 1 or greater now.

I hope I didn't confuse people but I've provided a little bit more clarity and my opinion on the use of this cutoff.

And that's coming in. How would you choose which PD-1 antibody to use for individual patients with HER2-negative disease? Well, right now we have 2 different antibodies that are approved. We have nivolumab and pembrolizumab. I think the activity between pembrolizumab and nivolumab is likely very similar. I think these drugs have the same mechanisms of action, basically. And some of the efficacy that we've seen in studies is probably just study design and patient population. I use nivolumab in my practice, largely because it's easier to pair nivolumab with FOLFOX chemotherapy. And in my practice, I use primarily FOLFOX, which is given every 2 weeks, and I can pair it easy with nivolumab, which is given either every 2 weeks or every 4 weeks.

The other question is, would you use zolbetuximab in HER2-positive disease? We have very active regimen for patients who have HER2-positive tumors. Most of patients with HER2-positive tumors also have PD-L1 expression of these tumors. So concurrent HER2 in PD-L1 expression was seen in 85% of patients in KEYNOTE-811 study. So no, I would not use zolbetuximab for these patients. The response rates are very high with FOLFOX, trastuzumab, and pembrolizumab. The regimen is well tolerated, so this is my go-to for patients who have HER2-positive and PD-L1-positive tumors. In those who have HER2-positive only, I use FOLFOX and trastuzumab per ToGA regimen, and I do not use pembrolizumab.

The next question is how to manage GI toxicity such as nausea and vomiting associated with zolbetuximab. That's a very good question. I think we will all have to learn how to use GI-associated toxicity with zolbetuximab in clinical practice. My site was not part of the clinical trial with zolbetuximab, so I don't have any hands-on experience with this drug. But our plan is to use rather aggressive and preemptive anti-nausea regimens. We will start patients on olanzapine before chemotherapy and continue probably for at least 5 days after the infusion. What I'm hearing from other experts in the field is that slowing down the infusion, interruption of the infusion during the first 2 treatments is sufficient to get patients through these treatments, although nausea can be quite significant. What I'm also hearing is that the GI toxicities improve and diminish significantly after the first 2 infusions.

The next question is: What is the optimal PD-L1 CPS cutoff to add pembrolizumab to trastuzumab chemotherapy in HER2-positive

disease? Well, as I referred to earlier, even though KEYNOTE-811 enrolled patients with HER2-positive tumors regardless of PD-L1 expression, subgroup analysis demonstrated that pembrolizumab primarily benefited patients that had tumors with PD-L1 CPS score 1 or greater. So that's a cutoff. I think it's going to be, hopefully over time, will get easier and PD-L1 CPS 1 of cutoff will become uniform across upper GI tumors and across different anti-PD-1 agents to simplify this issue. We are seeing repeatedly, across different studies in both HER2-positive and HER2-negative tumors, that the addition of anti-PD-1 antibodies do not benefit patients with tumors that have PD-L1 CPS score of less than 1. So in my opinion, 1% as a cutoff across these indications is appropriate and also simplifies our approaches.

Well, if there are no more, I'll thank everybody for your participation and for listening in and for these great questions. And we will continue to learn how to use these drugs in practice and have to make sure all of our patients are tested for these biomarkers. How to get all of this information in a timely manner is going to be a bit of a challenge as well over the next few months.

Thank you so much for your participation.

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