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Immune-Based Advances in Gastric, Esophageal, and Gastroesophageal Junction Cancers

Announcer:
Welcome to CME on ReachMD. This activity, entitled “Immune-Based Advances in Gastric, Esophageal, and Gastroesophageal Junction Cancers” is provided by Prova Education.

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Dr. Van Cutsem:
Recent immunotherapy approvals for gastric, esophageal, and gastroesophageal junction [GEJ] cancers have transformed the treatment landscape. We now have more options, and are able to achieve better outcomes for some patients. Do you know how to incorporate newly approved regimens and data into your practice?

This is CME on ReachMD. And I’m Eric Van Cutsem working in Leuven, Belgium. And here with me today are Dr. Elizabeth Smyth from Cambridge, UK, and Dr. Sunnie Kim from Colorado in the US.

Dr. Smyth:
Hello, thank you for having me today.

Dr. Kim:
Hi, there. Thank you for having me today, too.

Dr. Van Cutsem:
So let’s get started. Dr. Smith, Lizzy, to set the stage for this chapterized course, what do we need to know about the principles of biomarker testing?

Dr. Smyth:
Biomarkers are really critical in oncology. We generally divide biomarkers into two types: prognostic biomarkers which are really telling us intrinsically how a tumor might behave, and predictive biomarkers which really tell us how a tumor will respond, for example, to a particular treatment. So for example, we could take MSI, or mismatch repair deficiency, and it’s a prognostic biomarker in patients with resected, early-stage colon or gastric cancer, because those patients have good survival. And it’s also a predictive biomarker because it predicts that those tumors will respond well to immune checkpoint inhibitors.

When we think about biomarker testing, we generally think about looking at the tumor. For example, using tools like immunohistochemistry for proteins, or NGS sequencing for either single genes or patterns, like MSI. We also have biomarkers which are in the germline. So for example, DPYD testing for 5-FU toxicity or UGT1A1 for irinotecan.

When we think about the principles of biomarker testing, we want to know about the sensitivity of a biomarker. How good is it detecting something that’s there? The specificity, the positive predictive value for response, for example, with PD-L1 or the negative predictive value? So it’s a complex area, but really important for predicting survival and response to treatment in oncology.

Dr. Van Cutsem:
Thank you, Lizzy. Dr. Kim, what can you tell us about PD-L1 and HER2 overexpression?

Dr. Kim:
Yes, definitely. So PD-L1 is a protein that we can stain for in gastric and esophageal cancers. The score we use is something called the combined positive score [CPS]. And this is defined by the number of PD-L1-staining cells in the tumor and immune cells divided over the total number of viable tumor cells, and that's multiplied by 100. And that's how you come up with the score.

We know that the higher the score, the more likely immunotherapy agents such as PD-1 inhibitors like nivolumab and pembrolizumab will be effective. There was a first-line study for gastric and GEJ cancers, CheckMate 649, which showed that with the PD-L1 score of 5 and higher nivolumab was associated in combination with doublet chemotherapy with an improved survival rate compared to chemo alone. Similarly, in study KEYNOTE-590, we saw that the addition of pembrolizumab to doublet chemotherapy in PD-L1 CPS 10 or higher was associated with improved survival. Just be aware that these 2 studies did use different PD-L1 assays, but generally the higher the score, the higher likelihood there'll be a response to chemoimmunotherapy.

With HER2 overexpression, this is overexpressed in about 20% of gastroesophageal cancers. The HER2 overexpression is higher in the gastroesophageal junction and the gastric-cardia compared to more distal gastric cancers, and we also see it more overexpressed in the intestinal subtype versus diffuse subtype.

Interestingly, there is a considerable overlap between PD-L1 expression and HER2 overexpression. In one study it was 85%. And that makes combined HER2-directed therapies and immunotherapies very compelling combinations.

Dr. Van Cutsem:
Thank you. That's all very important and relevant information. And on top of that, we can say that on top of testing for PD-L1 and HER2, MSI, MSS testing is also extremely relevant. Although, however, only around 3% of patients with metastatic gastric adenocarcinoma do have an MSI-high or deficient mismatch repair tumor. This is indeed important because it may have profound implications also for the further treatment options. So HER2, PD-L1, and MSI testing are important.

And in the future, there may be some emerging biomarkers that are coming through because we now have some agents, indeed, that are under investigation in gastric cancer that target patients with tumors that overexpress FGFR. And if these ongoing trials would show a positive effect of the addition of the targeted agent in combination with chemotherapy, then we have to broaden our panel of markers that we test for. So this is important for the future outlook and treatment recommendations that we want to do.

And in Chapter 2 we will be discussing current treatment recommendations for metastatic gastric, esophageal, and GE junction cancers. So stay tuned.

Dr. Van Cutsem:
Welcome back. We were just talking about biomarker testing. And now we are going to discuss treatment focused on evidence-based guideline recommendations for metastatic gastric, GE junction cancers, and esophageal cancer.

So, Sunnie, what do evidence-based guidelines recommend for the treatment of metastatic gastric and GE junction cancers?

Dr. Kim:
The way I first divide it is between HER2-positive and HER2-negative cancers. So for HER2-negative cancers, we start with the doublet chemotherapy, which is our go-to fluoropyrimidine and a platinum agent. And for tumors with a higher PD-L1 score, we would add a PD-1 inhibitor based on CheckMate 649 and KEYNOTE-590 where they looked at nivolumab and pembrolizumab, respectively.

We know that the higher the PD-L1 score, the better chemoimmunotherapy works. In the US the FDA has approved the addition of PD-1 inhibitor without restriction; however, NCCN does recommend that a PD-1 inhibitor be added for tumors that have a PD-L1 score of at least 1. EMA [European Medicines Agency] has more strict guidelines where they require a PD-L1 score of 5 or higher for gastric and GEJ cancers to add a PD-1 inhibitor. And for esophageal cancers, a PD-L1 score of 10 or above.

For patients with HER2-positive disease in the US, the FDA did approve adding pembrolizumab to chemo plus trastuzumab. And this was based on interim results from KEYNOTE-811, which showed an improved overall response rate with the addition of immunotherapy. We are still awaiting final survival data from that study.

And really, the decision to have a patient receive second-line and beyond treatment is based on the performance status. As we know, many of these patients can clinically decline rapidly, and so the decision to give them second-line treatment is really based on the patient's performance status. Just a discussion about what to expect in terms of survival with second-line and beyond therapy. Options for HER2-negative disease include irinotecan; ramucirumab, which targets the VEGF-R2; paclitaxel or docetaxel; and more recently,

trifluridine/tipiracil.

For HER2-positive disease, after a long history of not being able to successfully treat these patients, we have trastuzumab/deruxtecan, which is an antibody-drug conjugate. And this is an option for patients with HER2-positive disease in the second-line and beyond setting.

Dr. Van Cutsem:
Thank you so much, Sunnie. This is clear. And, Dr. Smyth, what are the data telling us about HER2-targeted antibody-drug conjugates or, in other words, the ADCs?

Dr. Smyth:
Thanks, Eric. Well, I think that there's a lot of excitement around ADCs particularly initially in the second-line setting as Sunnie just mentioned. So just to recap, an ADC targeting HER2, for example, trastuzumab/deruxtecan, or T-DXd for short, is a trastuzumab-like antibody with chemotherapy attached to this, in this case deruxtecan, which infiltrates then into the tumor cell. And you've got 8 molecules of chemotherapy attached to a single trastuzumab molecule. So you've got a lot of effect on the tumor, but less effect systemically, hopefully, for the patient.

And what we see also with T-DXd is a bystander effect, which means that chemotherapy leaks out into the surrounding tissues within the tumor and also eliminates cells which are not HER2 positive. That's really important in gastric and esophageal cancer with HER2 positive because we know that HER2 expression is heterogenous, meaning that each cell does not express HER2.

So the studies that have looked at trastuzumab/deruxtecan so far are the DESTINY series of trials. The first trial that yielded a license in Asia and the US is DESTINY-Gastric01. In that study, patients who had previously been treated with chemotherapy and trastuzumab were randomized to either T-DXd or standard of care chemotherapy. And what we saw in that study, which was an Asia-only study, was that patients had a response rate of around 40%, a median overall survival of 12 months on T-DXd, which was substantially better than chemotherapy. So this led to the Asian and US license. But you know, often we see different responses in Asian patients than we do in non-Asian patients in gastric cancer trials. So I think those results were rightly needed to be validated in another trial.

So we have a study called DESTINY-Gastric02, which we've recently seen the results of – an updated result at ESMO 2022. And in that study, we had non-Asian patients. So US, European patients who were previously treated with chemotherapy and trastuzumab for HER2-positive gastric cancer. They had a biopsy before they were treated with trastuzumab/deruxtecan in this non-randomized study. And that's important because we know that about a third of patients lose expression of HER2 on their tumor after trastuzumab. And we think there's probably less value in treating those patients with trastuzumab-directed therapy in the second-line setting.

So in DESTINY-Gastric02, in the updated results, we saw a response rate of 42% and, again, a median overall survival of more than 12 months, which is really excellent when you compare it to the current standard of care, which is chemotherapy or chemotherapy and ramucirumab. It's not a registration trial in Europe. We do have an ongoing registration trial which is DESTINY-Gastric04, and that's comparing trastuzumab/deruxtecan to the standard of care, which is paclitaxel and ramucirumab. So that's currently recruiting. And we look forward to that really showing, hopefully, that this is an excellent option for patients in future.

We do also have ongoing studies in the first-line setting which are exploring combinations of T-DXd with various different chemotherapy drugs and immunotherapies, hopefully moving towards the first-line trial in future.

Dr. Van Cutsem:
All very important information. And so it shows that the field is moving and indeed it shows that biomarkers are extremely relevant to test – the HER2 testing, PDL testing. There are slightly different views, as you've heard already between what European oncologists or what EMA has approved for at least for the checkpoint inhibitors for nivolumab but more restricted label compared to the US's more broad label. And in a sense, future research will help us to clarify some of these aspects clearly in this setting. And that's important. And with that we can really, indeed, make our NCCN or ESMO recommendations and guidelines for, as well, HER2-targeted agents. And Lizzy also has mentioned some of the important aspects of trastuzumab/deruxtecan.

We also have the data in HER2-positive patients of pembrolizumab in combination with trastuzumab and chemotherapy, showing a clearly higher response rate in the KEYNOTE-811 study. That's not yet approved in Europe; that's approved in the US. We are awaiting final results on looking at PFS [progression-free survival] and OS [overall survival] from KEYNOTE-811 looking at the efficacy of trastuzumab/pembrolizumab in combination with chemo compared to trastuzumab chemo alone in this setting.

And then there are a couple of new HER2-targeted agents also that may help us to shape these treatment algorithms. So thank you for sharing this important information.

In Chapter 3, we will be discussing future treatment considerations. So stay tuned.

Dr. Van Cutsem:
For those just tuning in, you're listening to CME on ReachMD. I'm Eric Van Cutsem from Leuven, Belgium. And here with me today are Dr. Lizzy Smyth from Cambridge, UK, and Dr. Sunnie Kim from Colorado in the US. We're discussing immune-based advances in gastric, gastroesophageal junction, and esophageal cancers.

Welcome back. Now that we've discussed treatment recommendations, let's shift our focus to the future and consider what's in store for us and for our patients with gastric, GE junction, and esophageal cancers.

So, Dr. Kim, where are we headed with immune-oncology treatments?

Dr. Kim:
So it is quite an exciting time. Now that we have had multiple first-line and adjuvant studies showing benefit of immunotherapy, there are a number of studies underway exploring first combinations with IO and then of course really novel immunotherapy agents.

In the realm of combinations with known agents, you had mentioned FGFR2b; there's an antibody, bemarituzmab, that targets that. They're looking at the bemarituzmab in combination with a checkpoint inhibitor and chemotherapy in the first-line setting. Other targets like HER2, there is tucatinib which is a small molecule inhibitor of HER2, and that's also being studied in combination with chemoimmunotherapy. We did receive some preliminary safety and efficacy data looking at a tyrosine kinase inhibitor, lenvatinib, in combination with chemoimmunotherapy as well. It seemed to be tolerable and with some promising activity, but of course, we'll have to see how the larger study pans out.

And then there is another drug, DKN-01, which targets the Wnt signaling pathway. And that's also being studied in combination with chemoimmunotherapy.

In terms of where we're headed towards, you know, bispecific antibodies have been talked about a lot, especially in the hematological malignancies, and that is also a growing area of evaluation in gastric and esophageal cancers. Bispecific antibodies, they attach to 2 different antigens simultaneously. As an example, there's one where we have a bispecific antibody targeting Claudin 18.2, which is a very promising biomarker, as mentioned previously, which can be overexpressed in gastric cancer. And then another part that targets 4-1BB, and that is a potent stimulator of T cells and NK cells, hopefully producing a robust antitumor effect. That's undergoing clinical trial investigation right now.

And then car T cell therapy in solid tumors is becoming a reality, fortunately. CAR stands for chimeric antigen receptor, and it involves reengineering our own T cells to identify a protein of interest. And in the case of a recent presentation at ASCO, it was also targeting Claudin 18.2. And we saw some initial safety and efficacy for this therapy. And the promising initial response rate was almost 60%. But this was in just a handful of patients. So we'll have to see how that pans out in the future. But overall, we're seeing a lot of trials with combinations with known immunotherapy drugs, and then more novel ways for us to target the immune system.

Dr. Van Cutsem:
Very interesting information, Sunnie. Lizzy, what else do you have to add of new directions?

Dr. Smyth:
I think that Sunnie has covered most of those. I think really important for us to understand with these novel combinations, for example, FGFR2b, Claudin 18, and second-generation targets like TIGIT, is what is the immune context of these tumors? So for example, in using a PD-1 inhibitor with an FGFR inhibitor, does the tumor need to be FGFR2b and PD-L1 positive for maximal efficacy? And I think that's important, especially when we'd probably be considering double antibody therapies in future which have a financial toxicity as well.

So I think the lead stage is well covered there. What I'm really excited about is moving these into the earlier-stage setting. At the moment using perioperative chemotherapy and surgery, we cure a maximum of 50% of our patients. So we want to do better.

So there have been a number of studies that have combined checkpoint inhibitors with chemotherapy. The first results of these we've seen the AIO DANTE study which was atezolizumab and FLOT. And what we saw was complete pathological responses were improved in patients, as you might expect, whose tumors expressed PD-L1 at high levels. So there are a number of different studies that we're waiting on. For example, KEYNOTE-585, a larger cohort from AIO DANTE, which will now go to phase 3, and the MATTERHORN study. So those are going to inform our practice in the perioperative setting in future.

The other group of patients who I'm particularly excited about would be MSI tumors. I think that we should see a registration trial in the first line for a chemotherapy-free option, for example, perhaps with a PD-1, CTLA-4 antibody. There are novel combinations emerging, but also operable MSI tumors. So we've seen the results of the NEONIPIGA study, which was a French study in which patients with operable MSI tumors were treated with neoadjuvant nivolumab and ipilimumab; 60% of those patients had a pathological complete response. Those patients went on to surgery. But the next step is really whether these patients need to be operated on at all. And that's

going to be evaluated in trials in future. So that's a group of patients where we could, in fact, move to a surgery-free option which is very exciting.

Dr. Van Cutsem:
Thank you so much. So the bottom line message is that, really, we have, as a society, to invest in research to understand much better the role of these different biomarkers, the role of these different agents in order to improve the outcome for patients. And as Lizzy said also, moving this also from later lines of treatment towards neoadjuvant and perioperative setting, because if you can show that in this setting these targeted agents increase the efficacy of perioperative chemotherapy in combination with an operation, then we will be able to cure more patients.

And gastric cancer remains a very frequent problem. We need really to improve on the global survival rates, and we need to cure more patients. And the in-depth knowledge is investing in research and in the increase in depth knowledge may help us to do that really.

So in Chapter 4 we will be discussing regional considerations in testing and treatment. Stay tuned.

Dr. Van Cutsem:
Welcome back. We just looked at what the future may hold for gastric, GE junction, and esophageal cancers. Now let's talk about what testing and treatment look like in different regions. And it's good that we have an international panel as I am going to ask the first question to Lizzy from Cambridge in the UK. How does the global incidence of these cancers vary?

Dr. Smyth:
Oh, thanks. That's a really interesting question. So if we think about gastric cancer in general, this is a cancer which is very, very common in East Asia. And for that reason, patients in East Asia, for example, Japan and Korea, frequently undergo screening for gastric cancer. And those cancers are detected early, and those patients have surgery in those countries.

Gastric cancer in contrast, where I work, and perhaps where you work, Eric, is less common than junctional adenocarcinoma, or tumors of the GE junction. So that has a different epidemiology and etiology. We know it's associated with kind of a more Western lifestyle and, for example, Barrett's esophagus and reflux, 70% of what I see are junctional adenocarcinomas. Unfortunately, at the moment, we don't screen for that, although we're moving towards developing screening tools that are not endoscopy. For example, Cytosponge that can be used in a GP surgery.

So it's not so much the histology that differs by region, rather, but sort the site of the cancer. And the site of the cancer really does impact on the diagnosis and on the treatment. So when we see tumors in Western countries, non-Asian countries, these junctional tumors, unfortunately tend to present quite late because we don't have those screening programs. So patients might present with dysphasia, they undergo an endoscopy, and sadly, only about 50% of patients are able to have a potentially curative surgery. A lot of our patients are diagnosed at a late stage.

In terms of the variability in testing, I'm not sure that we should see a variability in testing. We do see variation in what's in the licensing situation, for example, FDA versus EMA versus Japan, Korea, other Asian countries. But I think all of the underlying biology of these cancers is very similar. If we think of gastric adenocarcinoma, not the diffuse type, but really the chromosomally unstable subtype, intestinal type, as Sunnie mentioned before, it's really a biological continuum between the lower esophagus, the GE junction, and those gastric cancers. So the chromosomally unstable, most of them are p53 mutant, we see about 20% to be positive for HER2, although that is more common at the junction. We see 3% to 5% of advanced gastric cancers being mismatch repair deficient. Although that's more common in distal tumors, it's also present in tumors at the junction. So even for those junctional cancers, we need to test for a mismatch repair deficiency.

And I'm not aware of massive differences in PD-L1 score between Asian and non-Asian patients. So if I had a message, the message would be gastric cancers, more common in East Asia, although probably make up 40% to 50% of tumors in Europe. Junctional tumors, more common in Western Europe, the US, Australia, but the biomarker testing should be universal.

Dr. Van Cutsem:
Thank you, Lizzy. All very interesting aspects. Sunnie, can you expand upon the variability of histology by region that Lizzy just mentioned?

Dr. Kim:
Similarly to what you're probably seeing in Europe, a lot of the gastroesophageal cancers that I treat are mostly at the junction, the GE junction. And a lot of this is due to, unfortunately, these Western habits, obesity, GERD. We don't see a lot of squamous cell cancer in the US, as these are typically associated with smoking and drinking, and smoking has really fallen out of favor in the US. But being able to practice in the US, it's a very diverse population. I see patients from really all over the world, and depending on what city you practice

in – most of my patients are actually East Asians and from central South America. And those patients typically have more distal gastric cancers.

And then one thing I did want to touch upon was there was some talk about variability of testing. I agree that testing should probably not be variable. The MMR testing the HER2 and the PD-L1 are pretty standard. I think it's important that we really do focus on making sure we capture the patients who have MMR-deficient tumors, because there was recently the pembrolizumab EU approval for MSI high mismatch repair deficient gastric cancer. This was already approved in the US, and this is for patients eligible for second-line and beyond treatments. And in this study, we found that patients with MMR-deficient gastric cancer, those patients had a 30% response rate in the second-line and beyond setting, which is quite notable compared to standard chemotherapy or chemo plus ramucirumab in a second-line setting. So it's important to identify these patients as soon as possible so that they can be offered immunotherapy.

What's nice is that with these first-line chemoimmunotherapy approvals, hopefully we are capturing a lot of these patients, but really these immunotherapy approvals probably should be moved to the first-line setting for the MMR-deficient and MSI-high gastric cancer.

Dr. Van Cutsem:
Thank you. Well, this has certainly been a fascinating conversation. And we can summarize this with a couple of key takeaway messages. One, every oncologist has to understand the relevance of biomarker testing today in these cancers. MSI, MSS testing, HER2 testing, and PDL testing is important. Other emerging biomarkers are coming through, and we see a whole new armamentarium of new agents – HER2-targeted agents, even oncology agents – that we are able to use and that improve the outcome of patients with metastatic disease. And hopefully, after all this, we see some studies also in resectable disease in more early stages. So progress is clearly being made for patients with gastric, GE junction, and esophageal cancers.

Unfortunately, that's all the time we have today, so I want to thank our audience for listening in and thank both Dr. Lizzy Smyth and Dr. Sunnie Kim for joining me and for sharing their very valuable insights. It was great speaking with you today.

Dr. Kim:
Well, thank you so much for having me. It was a great discussion.

Dr. Smyth:
Thanks for having me. That was a really interesting discussion on gastric and gastroesophageal cancer. Hope to see you again sometime.

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