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Bringing Treatment Into Focus: Biomarker-Driven First-Line Therapy for Metastatic Gastric/GEJ Cancers

Announcer:
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Chapter 1

Dr. Kim:
This is CME on ReachMD, and I'm Dr. Sunnie Kim from University of Colorado Cancer Center.

Dr. Ilson:
And I’m Dr. David Ilson from Memorial Sloan Kettering Cancer Center in New York.

Dr. Kim:
Today, we are reviewing a case and discussing first-line treatment options for patients with HER2-negative PD-L1-positive metastatic gastric/GEJ adenocarcinoma. Let's start our discussion with a patient case.

So this is a 62-year-old man with a history of dark stools and reflux symptoms. An upper endoscopy was done showing a large infiltrative and ulcerated non-circumferential mass in the lesser curvature of the stomach, with stigmata of recent bleeding. Biopsy was done and pathology showed invasive adenocarcinoma with signet ring cell features. The CT of the chest, abdomen, and pelvis showed the concentric soft tissue density thickening of the gastric antrum, but no obvious metastatic disease.

As is our institutional guidelines, diagnostic laparoscopy was done and unfortunately showed peritoneal nodules. Biopsy confirmed signet ring adenocarcinoma consistent with the patient's primary gastric primary. Biomarker testing was performed. HER2 IHC was 0, PD-L1 combined positive score was 6, and claudin 18.2 IHC, which we would normally do at our institution, was 1+ in 30% of the cells. The patient was started on FOLFOX plus nivolumab and he experienced stable disease for 9 months on CT imaging.

Now, I’ll review clinical data on first-line treatment options for patients with HER2-negative, PD-L1-positive metastatic gastric and GEJ adenocarcinoma. The topics of discussion will be 2 major clinical trials: The CheckMate 649 trial included nivolumab with chemotherapy and KEYNOTE-859, which is chemotherapy plus pembrolizumab. And then finally, I'll be discussing the current guideline updates for first-line treatments of PD-L1-positive gastric and GEJ adenocarcinoma.

So the first study is CheckMate 649. This was a randomized open-label global phase 3 study. Patients needed to have untreated, unresectable advanced or metastatic gastric GEJ or esophageal adenocarcinoma, HER2 needed to be negative, and ECOG 0 to 1. The patients were randomized initially to 3 arms: nivo plus XELOX or FOLFOX, chemotherapy with XELOX or FOLFOX, and then the third arm, which was discontinued, was the nivo plus ipi arm.

The stratification factors included, at that time, tumor PD-L1 expression, Asia versus United States and Canada versus the rest of the world, ECOG status, and chemotherapy, XELOX versus FOLFOX. There were dual primary endpoints, overall survival and progression free survival, and the PD-L1 CPS greater than or equal to 5. And then secondary endpoints included OS and PFS and response rate in other PD-L1 CPS groups. And then exploratory endpoints included safety and quality of life.

So these are the results from the 36-month follow-up. In terms of overall survival, we found that in a PD-L1 CPS greater than 5, there was a significant overall survival benefit of 14 months versus 11 months in the nivo plus chemo arm versus chemo alone, and then all randomized, there continued to be a survival benefit, although less dramatic at 13.7 months versus 11.6 months.

In looking at the response and the duration of response for patients with PD-L1 CPS greater than or equal to 5, we did find that there was a higher response rate of 60% versus 45% in the chemo plus nivo arm versus chemo alone. And in all randomized, also, there was a response rate benefit of 58% versus 46%. As you can see, there is a tail of the curve, although it's a minority of patients, about 10% of patients. And then looking at overall survival and objective response rate based on PD-L1 CPS, we find that as the CPS score improves or goes higher, there seems to be improved survival with response rates not seeing as much of that trend, but certainly we are seeing the highest response rate in the tumors that have PD-L1 CPS greater than or equal to 10 with the chemo plus nivo arm.

And then going into KEYNOTE-859, this was looking at chemo plus pembro in the same population. Again, this was looking at patients who had received no prior treatments. They needed to be locally advanced unresectable or metastatic stomach or GEJ adenocarcinoma, needed to be HER2 negative, and they were randomized 1:1 to doublet chemo plus pembro or chemotherapy alone. The primary endpoint here was overall survival. Secondary endpoints were PFS, response rate, duration of response, and safety.

And what we find is very similar to what we saw in CheckMate 649 is that in the overall population, there was an OS benefit of 12.9 months versus 11.5 months with a hazard ratio of 0.78. But as the PD-L1 CPS goes higher in the middle, we see CPS greater than or equal to 1. We see more of a benefit with a decreasing hazard ratio of 0.74. And then with the PD-L1 CPS greater than or equal to 10, the hazard ratio is 0.65 where we see the biggest benefit in survival, 15.7 months versus 11.8 months.

And looking at survival in subgroups, nearly all subgroups benefited from the addition of pembrolizumab with chemotherapy in PD-L1 CPS greater than or equal to 1 and PD-L1 CPS greater than or equal to 10. Secondary endpoints included PFS, response rate, and duration of response. What we find here, this is specifically the PFS in the Kaplan-Meier curves, we found that, again, when the PD-L1 CPS increases, we find that the hazard ratios continue to decrease. And so the higher the PD-L1 CPS, we see improvements in the progression-free survival.

So currently, guideline recommendations from the NCCN are a bit complicated, and it really depends on whether you're using nivo plus doublet chemo or pembrolizumab plus doublet chemo. So for the HER2-negative population for our gastroesophageal cancers, for nivolumab NCCN recommends a category 1 recommendation for the use of nivo plus doublet-chemo if the PD-L1 CPS is greater than or equal to 5. When considering pembrolizumab, there's a category 1 recommendation if the PD-L1 CPS is greater than or equal to 10, and a category 2B recommendation if the PD-L1 CPS is 1 to 10. We do not recommend the use of pembrolizumab plus chemotherapy for PD-L1 CPS of 0.

I also brought up the ASCO guideline recommendations too, which are quite similar to the NCCN recommendations. For patients with HER2-negative gastric adenocarcinoma, there's a strong recommendation to add nivolumab to doublet chemotherapy for PD-L1 CPS greater than or equal to 5. But as you can see, there are some qualifying statements here. If the CPS is 1 to 5, the addition of nivolumab to doublet chemotherapy can be considered on a case-by-case basis, and for patients with a PD-L1 CPS of 0, ASCO guidelines do not recommend the addition of nivolumab.

And further down, when we look at HER2-negative esophageal or GEJ adenocarcinoma, the use of nivolumab to doublet chemotherapy is recommended for CPS greater than or equal to 5, and if a practitioner wants to add pembrolizumab to doublet chemotherapy, the recommendation is to use a cutoff of CPS greater than or equal to 10.

So in terms of discussion questions, I think, for David, obviously, we've debated this over and over again in the field, but what is the optimal PD-L1 CPS cutoff for nivo or pembrolizumab to doublet chemotherapy? And then it leads into the next question: Does it matter which PD-L1 antibody we use?

Dr. Ilson:
Yeah. Well, I think there are different criteria for different studies. In the early pembrolizumab trials, they looked at a differential of greater than or equal to 10% or less than 10%. So for the original KEYNOTE-590, PFS and survival benefits were really limited to patients that tested CPS 10% or higher. Patients that were less than 10%, it was no clear progression-free or overall survival benefit. But they didn't look into ranges between 1% and 9%. That was done subsequently in KEYNOTE-859 where they did demonstrate

survival benefits when you looked at the 1% to 9% range. So it may be that the 10% for adenocarcinoma for pembro is a little stringent, and that for the KEYNOTE-859, it demonstrated not only a benefit for greater than or equal to 10%, but also benefits in the 1% to 9%. What they didn't do in that analysis was break it down by greater than or equal to 5%.

The nivolumab studies were designed with the primary endpoint of looking at CPS greater than or equal to 5% and clearly met that endpoint. So I think for nivolumab, a greater than or equal to 5% CPS score indicates progression-free and overall survival benefits. Less than 5%, there really is an uncertain benefit, and that's why we have given a recommendation of Level 1 for greater than or equal to 5%, 1% to 4% is Level 2B, and then negative, CPS negative, we would not recommend checkpoint inhibitors.

For pembrolizumab, the original designation of the 10% cutoff can be modified now given the data from 859, showing a potential benefit for 1% to 9%. We've had discussions potentially trying to harmonize this across trials where this 5% cutoff seems to be the most consistent for identifying a benefit. So I think 5% or higher would be the most consistent cutoff. 1% to 5%, we make a case-by-case determination. Less than 1%, there's not a clear benefit for adding a checkpoint inhibitor.

Dr. Kim:
Yeah. I totally agree with the need to harmonize these PD-L1 cutoffs because I think we also know that the PD-L1 antibodies are different, the 28-8 versus the 22C3. There's some data that perhaps the 28-8 may be more sensitive than the 22C3. But it's hard because the oncologist, when faced with doing the PD-L1 testing, they don't always have a choice of which antibody to use. And so I think, again, this highlights the need to really harmonize these PD-L1 cutoffs to make it easier for the practitioner to know when to use an immune checkpoint inhibitor with doublet chemo.

Dr. Ilson:
Well, I think the nivolumab studies have consistently shown a higher percentage of PD-L1-positive patients, so they're picking up more patients with the antibody used.

Dr. Kim:
Okay. So that's a 28-8 then, as opposed to 22C3. Yes.

Dr. Ilson:
But the more recent pembro studies have also suggested a higher percentage of positive patients. It used to be up to 50% to 60% were PD-L1 negative. In the more recent studies, up to 60% or more have some degree of PD-L1 positivity. So I think hopefully we can harmonize the guidelines and agree, at least for adenocarcinoma, that the 5% should be a consistent cutoff across drug types. And again, individualizing the use of drugs for patients that are in the 1% to 4% range.

Dr. Kim:
And then another question is, do you ever re-biopsy to check for PD-L1? So say if it was PD-L1 0 in the beginning, would you ever reconsider rechecking again? Because we know that this is a dynamic biomarker.

Dr. Ilson:
Yeah. We have to remember, this is always one of the arguments for not being too rigid, because any biopsy is a random sample. So I think there's evidence clearly for HER2 that we probably should re-biopsy patients when they're later on in the course of treatment, because a significant percentage of patients lose HER2 expression. Re-biopsy for PD-L1 has not really been validated, and the problem is that once they're progressing on first-line treatment, at least for adenocarcinoma, we don't have the option of using checkpoint inhibitors in later-line treatment.

Dr. Kim:
Well, with that our time is up. We hope that you found the information helpful to you and your practice. Thanks for listening.

Chapter 2

Dr. Ilson:
This is CME on ReachMD and I'm Dr. David Ilson from Memorial Sloan Kettering Cancer Center in New York.

Dr. Kim:
And I'm Dr. Sunnie Kim from University of Colorado Comprehensive Cancer Center.

Dr. Ilson:
So with this case presentation, we're going to review first-line therapy in metastatic gastric and GE junction adenocarcinoma, specifically focusing on a patient who is HER2 negative, PD-L1 negative, but tests positive for the new biomarker claudin 18.2.

So I think we're going to start the discussion with a case. MJ is a 60-year-old man with a history of *Helicobacter pylori*-positive gastritis 5

years ago, which was treated and monitored for clearance. He presents now with anemia, epigastric pain with eating, and a 25-pound weight loss. Upper endoscopy shows a fungating mass in the gastric antrum, and a biopsy shows poorly differentiated adenocarcinoma. A CAT scan unfortunately shows 3- to 5-cm bilobar hepatic metastases, a gastric wall mass, perigastric and retroperitoneal lymph node metastasis consistent with metastatic disease.

Past medical history is notable for hypertension and elevated cholesterol. His ECOG performance status is 1 and laboratory evaluation was within normal limits.

In 2024, it's obligatory that we do biomarker testing before making a treatment decision. And we'll talk about this shortly, but there are 3, now probably 4, immunohistochemistries that are mandatory to guide treatment.

So his tumor test is HER2 negative by IHC. It is mismatch repair protein proficient. The PD-L1 score tested negative with a combined score of less than 1%, and claudin 18.2 was positive with 90% of tumor cells testing positive. We also got next-generation sequencing done by blood-based profiling, which indicated a P53 mutation, a microsatellite stable tumor, and that the tumor was HER2 non-amplified.

So in reviewing the data, what is the optimal chemotherapy and targeted agent? Should we consider FOLFOX plus pembrolizumab or nivolumab, or should we use FOLFOX plus zolbetuximab?

So what are the minimum biomarkers that we have to test in a newly diagnosed metastatic gastric cancer? This is really obligatory in 2024. All patients require IHC for HER2. If IHC is positive at 3+ we can stop; if IHC is negative then we do FISH testing. Then we have to test, now, every patient for DNA mismatch repair protein deficiency. About 7% of gastric cancers are positive. Esophageal and GE junction cancers, the positivity rate is lower, hovering around 1% or less. These are patients that have exquisite responses to checkpoint inhibitors.

And then lastly, the IHC for PD-L1 where we use the combined score of the tumor macrophages and lymphocytes. We can now add a new biomarker, a fourth biomarker to first-line testing IHC for claudin 18.2. This will become a new standard. In the trials that were done, it was declared positive if 75% or more of cells tested positive. And then next-generation sequencing we also consider now in all patients with metastatic disease, either blood-based or tissue-based testing.

Where does zolbetuximab come in? Claudin 18.2 is an exciting new target in gastric cancer. It's a gap junction protein that's only expressed in the stomach and in gastric adenocarcinomas, and it is overexpressed in the vast majority of gastric adenocarcinomas. Zolbetuximab is a first-in-class monoclonal antibody that targets claudin 18.2, and it’s thought to work by an immune-mediated mechanism. It may stimulate antibody-dependent and complement-dependent cytotoxicity. The drug by itself does not appear to have significant activity.

However, there were 2 pivotal trials of zolbetuximab added to first-line chemotherapy in metastatic gastric and GE junction adenocarcinomas. The first was SPOTLIGHT, which was a global, randomized, double-blind, placebo-controlled trial in which patients had to test positive for claudin 18.2 75% or higher. And then patients were randomized to conventional FOLFOX, which was given on an every-2-week schedule, or zolbetuximab cycled on an every-3-week schedule. The primary endpoint of SPOTLIGHT was progression-free survival.

So progression-free survival by independent review was significantly improved for zolbetuximab over the chemotherapy alone, with a nearly 2-month improvement in progression-free survival with a hazard ratio that was statistically significant. And overall survival was also statistically significantly improved with a nearly 2-and-a-half-month improvement in overall survival combining zolbetuximab with chemotherapy compared to chemotherapy alone.

The secondary endpoint of response rate was similar. There was a more durable response seen in the zolbetuximab-treated patients, so even though there was not a difference in overall response rate, the duration of response and durability of response was higher and again, progression-free and overall survival were improved and met the primary endpoints of the trial.

So the second trial globally for zolbetuximab in claudin-positive metastatic gastric and GE junction adenocarcinomas was GLOW. This was a trial using capecitabine oxaliplatin as the chemotherapy backbone, cycled every 3 weeks in combination with zolbetuximab. And this was also a double-blinded, placebo-controlled, randomized, phase 3 trial.

Here we can see that progression-free survival was significantly improved for the addition of zolbetuximab of about 2 months compared to chemotherapy alone, which was statistically significant. And overall survival was also significantly improved by a little bit more than 2 months, favoring the addition of zolbetuximab to chemotherapy over chemotherapy alone. And what is impressive is that there seems to be a durable tail on the curve in patients that continued treatment.

Similar to the SPOTLIGHT trial, response rates were similar for the control arm versus adding zolbetuximab to chemotherapy, but again, the durability and tail on the curve for response duration favored the zolbetuximab arm.

So I think based on these positive global two phase 3 trials, we will likely see imminent approval of zolbetuximab in the first-line treatment of metastatic gastric and GE junction adenocarcinomas and, again, patients that test positive for claudin 18.2 with a positivity rate of 75%. The drug now is approved in Japan. It's awaiting approval in the US. There have been some manufacturing issues, but we anticipate that approval will be forthcoming, and this will represent a new first-line treatment option for patients with metastatic gastric and GE junction adenocarcinomas that test positive for claudin 18.2.

So the case that we appoint in this discussion was a PD-L1-negative patient. So the use of checkpoint inhibitors, we could argue, would not help that patient. So, Sunnie, what would be your approach to this patient, assuming that we now have approval for zolbetuximab, which is likely to be imminent?

Dr. Kim:
Well, for the patients who are PD-L1 negative, certainly with claudin-positive tumors, I would prefer FOLFOX plus zolbetuximab here. The lack of a response rate benefit was disappointing to see. Although, with the survival benefit, it would make me obviously choose that option.

But I think you're also asking, if the tumors like PD-L1 positive, how should we approach those patients? So I think if it's PD-L1 CPS greater than or equal to 5, I probably would go more with the chemo PD-L1 inhibitor approach. I think we see more data there. We see that tail in the curve. 10% of patients are benefiting. Also, we're seeing an improvement in response rate, and I think, although we talked about PFS and OS, I think an improved response rate is still very important. Many of these patients come to us very ill, and to try to get as much of a deep response as possible will probably benefit them moving forward, at least from a clinical perspective.

Dr. Ilson:
Now, I think in an initial retrospective analysis of the SPOTLIGHT patients, a small percentage were actually PD-L1 positive; it was only about 13 to 15%. I think larger series have suggested there's more overlap, that up to 40% to 50% of claudin-positive patients will also be PD-L1 positive, so we will have a choice now. But I think, clearly in the low PD-L1 patients where we're not likely to see a benefit from the nivolumab or pembrolizumab and a patient tests strongly positive for claudin 18.2, zolbetuximab will represent probably the preferred targeted agent to use once it's approved.

What's going to be a more difficult decision, as you outlined, is that patient that's CPS PD-L1 positive 5% or higher, should we go with first-line checkpoint inhibitor or first-line zolbetuximab? We're not going to have the luxury of using either drug later line because, right now, checkpoint inhibitors are only approved first line in metastatic and GE junction cancers. And zolbetuximab, as well, is really a first-line drug. So I think the 1% to 5% PD-L1-positive patients, that's an equivocal range. Do we see benefit for checkpoint inhibitors? But we're probably not going to see a randomized trial comparing the 2 drugs in first line. That's probably not going to be feasible.

What's going to be exciting is whether combining the drugs has any utility, because remember zolbetuximab does work by an immune-mediated mechanism. It uses immune recruitment, it's not a cytotoxic antibody by itself, but it's thought to result in, again, ADCC and CDCC that complements cytotoxic chemotherapy. And even with not seeing the response differential, we do get this 10%-15% higher response rate when we add a checkpoint inhibitor to chemotherapy over chemotherapy alone that we don't see with zolbetuximab, but it does seem that PFS and survival incremental benefits are quite similar for the use of these targeted agents in first line.

So I guess we can talk a little bit about toxicity management for these drugs. We've all become amateur immunologists with the use of immune checkpoint inhibitors now, managing sort of lower grade toxicities, mild skin toxicities, hypothyroidism, even toxicities like pneumonitis and nephritis, we know how to manage with steroids but usually can't rechallenge patients with checkpoint inhibitors.

Zolbetuximab, significant because, again, this is a target that's overexpressed in the stomach and in gastric cancers. There is targeted organ toxicity. We do see increased rates of nausea and vomiting as a toxicity when we combine zolbetuximab with chemotherapy compared to chemotherapy alone, and it really requires very aggressive multi-agent antiemetic prophylaxis to really reduce that risk.

What have you seen in your practice? Of course, the drug's not approved yet, but in the context of trial usage, how best to manage the toxicities with zolbetuximab?

Dr. Kim:
Yeah. Well, I think what's different about the nausea/vomiting with zolbetuximab is that it happens immediately in the chair, and so we really need to educate our infusion center staff, the nurses especially, about what should we do when the patient is having vomiting in the chair. And the recommendation is to stop, slow down the infusion, and then potentially retitrate up if the patient is tolerating it well. But my personal practice will be to really maximize the antiemetic regimen, so we avoid that situation to begin with, because slowing

down infusion to half-rate is very difficult to do in these packed infusion centers. Logistically it's difficult, so my approach will be to be very heavy-handed from the from the prophylactic standpoint. And the other thing that I think is nice is that we have these 2 different options for the PD-L1-positive and claudin-positive tumors. So say if you're having immune-related side effects to the checkpoint inhibitor and it becomes prohibitive to use, you may be able to add zolbetuximab as another option. And I do agree that in real life, we're probably seeing more of an overlap. Some of the real-world retrospective studies are seeing an overlap of upwards to 20% to 25%. So I think we'll have that option and that'll be nice to have.

Dr. Ilson:
Yeah, I think we're all awaiting approval of this drug so we can add to the armamentarium of use of these agents in first-line treatment to improve outcome for patients. And I think the exploitation of these targeted approaches, whether it's immune checkpoint inhibitors, now claudin 18.2 targeted by zolbetuximab.

And we have hope for other targets in the future like FGFR and other targets that are overexpressed. And again, to emphasize the use of next-generation sequencing, we always identify potential rare targetable mutations like BRAF V600E or NTRK or RET, for which we have tumor agnostic approval of different agents. But it certainly is an exciting time, and I think this case indicates, certainly in a PD-L1-negative patient that's claudin positive, once we have the drug available first line for such a patient, we'd likely combine either FOLFOX or capecitabine oxaliplatin with zolbetuximab.

With that, our time is up. We hope you can apply what you learned today to your practice. Thanks for listening.

Chapter 3

Dr. Kim:
This is CME on ReachMD and I'm Dr. Sunnie Kim from University of Colorado Cancer Center.

Dr. Ilson:
Yes, I'm Dr. David Ilson from Memorial Sloan Kettering Cancer Center in New York.

Dr. Kim:
Today we're reviewing a case and discussing treatment options for patients with metastatic gastric GEJ adenocarcinoma and multiple targetable biomarkers. Let's start a discussion with our patient.

So this is a 71-year-old man with new trouble swallowing and dysphasia found to have iron deficiency anemia with a hemoglobin of 8.1. An upper endoscopy showed a large fungating mass with bleeding in the lower third of the esophagus at 35 cm. Biopsy was done with pathology showing well-differentiated adenocarcinoma.

The CT chest/abdomen/pelvis showed a GE junction lesion extending to the gastric fundus and body. There were multiple enlarged mediastinal and upper abdominal lymphadenopathy with hepatic metastases.

Biomarker testing was done with HER2 IHC being 3+. A PD-L1 combined positive score of 2. The patient was started on FOLFOX plus trastuzumab plus pembrolizumab. He experienced improvement in his dysphagia after the first cycle, and the CT chest/abdomen/pelvis after 3 months showed a partial response with decrease in size of the hepatic metastases.

So let's turn to the clinical data on first-line treatment options for metastatic gastric and GEJ adenocarcinoma with multiple positive targetable biomarkers. So I'll be discussing 2 major studies: KEYNOTE-811, which looked at the addition of pembrolizumab to doublet chemo plus trastuzumab, and ToGA, which looked at the addition of trastuzumab to doublet chemotherapy. And then finally, going over the guideline updates.

So ToGA, this was published back in Lancet in 2010. This was a phase 3, randomized, open-label, international, multicenter study, and they screened almost 4,000 patients. And 800 of them, about 20%, were HER2 positive. And the definition for HER2-positive at that point was any FISH positivity or IHC positivity.

The patients were then randomized to receive 5-FU or capecitabine plus cisplatin, or 5-FU or capecitabine plus cisplatin plus trastuzumab. And what we found there was that OS was improved in patients with high HER2 expression, and they found that the subset of patients that experienced the most benefit were those with IHC 2+ FISH-positive tumors, or IHC 3+. When we look at the Kaplan-Meier curve, we see that for the patients who received trastuzumab plus chemotherapy versus chemotherapy alone, the median overall survival was 16 months versus 11.8 months. So based on that, it's standard to use trastuzumab plus chemotherapy for patients with IHC 2+ FISH-positive or IHC 3+ tumors.

And then subsequently, we have the KEYNOTE-811 study, which was looking at patients with no prior systemic treatment for advanced unresectable gastric and GEJ adenocarcinoma. They needed to be HER2 positive by central review, again, IHC 3+ or IHC 2+ and ISH

positive. And patients were randomized 1:1 to receive pembrolizumab, the 200 mg every 3 weeks, plus trastuzumab and doublet chemotherapy, or to receive placebo plus doublet chemotherapy. The dual primary endpoints were OS and PFS, and secondary endpoints included response rate, duration of response, and safety. For stratification factors, geographic region was considered, PD-L1 CPS less than 1 and CPS greater than 1, and also the chemotherapy choice.

So there were interim results of KEYNOTE-811 that were quite exciting, showing that, regarding the response rate in the pembrolizumab group, the response rate was 74% versus 51% in patients who had received just chemotherapy plus trastuzumab. Disease control rate was also higher at 96.2% versus 89.3%. There were a higher number of complete responses and partial responses in the pembrolizumab group, and based on this, there was an FDA approval to add pembrolizumab to chemo plus trastuzumab for the treatment of first-line advanced unresectable HER2-positive gastroesophageal adenocarcinoma.

And as we've been getting more data, we have found that the PD-L1 CPS matters. In 2023, Dr. Janjigian published in *Lancet* and found that for tumors with CPS less than 1, there was a lack of a PFS benefit. In addition, we have third interim overall survival analysis formally presented showing that for all patients there was a benefit in the third interim of OS with the pembrolizumab group over the placebo group. And we found that the survival was accentuated in the PD-L1 CPS greater than or equal to 1. And then we did find out on May 1st that the KEYNOTE-811 met its dual primary endpoint of overall survival and PFS, and we expect those results to be formally presented at the ESMO International Conference happening this month.

So currently when we look at the NCCN Guideline recommendations for patients with HER2 overexpressed gastric and esophageal adenocarcinoma, there is a category 1 recommendation to add pembrolizumab for PD-L1 CPS greater than or equal to 1.

So in summary, ToGA, in 2010 established that doublet chemotherapy plus trastuzumab was a standard first-line therapy for HER2-positive gastroesophageal adenocarcinoma. And following up on that, KEYNOTE-811 showed positive findings in both PFS and OS with the addition of pembrolizumab with doublet chemotherapy and trastuzumab for PD-L1 CPS greater than or equal to 1 disease.

So going into our discussion, obviously a lot of this information with KEYNOTE-811 is upcoming with the ESMO international conference, but curious to get your thoughts, David. This was a statistically significant finding in terms of OS and PFS, but what are your thoughts about whether this is a clinically meaningful result with the addition of PD-L1 inhibition to trastuzumab plus first-line doublet chemotherapy?

Dr. Ilson:
Yeah. Well, I think the initial presentation of a response rate approaching 75% was unprecedented in gastric cancer and really a stunning result that at the time led to conditional approval of pembrolizumab combined with first-line treatment. So and this was a rare situation in which the phase 3 trial actually seemed to duplicate results that were seen in the phase 2 trial signal.

So with longer follow-up, the trial did achieve its endpoints and with significant improvement in progression-free survival, and now with longer follow-up we are seeing a significant overall survival benefit of 2 to 3 months, which is clinically meaningful.

So I think the dramatic improvement in response – we talked about this in other cases, that the higher response rate likely is going to translate into more clinical benefit for patients. These are often very symptomatic patients with upper GI symptoms, pain complaints. And to have this degree of antitumor activity in gastric cancer is really unprecedented and a significant gain above trastuzumab and chemotherapy alone and with the trastuzumab really not adding any meaningful toxicity. And we now know how to manage the immune-related side effects and the CPS cutoff for benefit seems lower for the HER2 patients. So we have 1% or higher that seem to benefit with the addition of pembrolizumab to trastuzumab plus doublet chemotherapy. So I think this really has changed practice in HER2-positive patients, that the patient should get doublet chemotherapy, typically FOLFOX or capecitabine oxaliplatin with trastuzumab and pembrolizumab as first-line treatment, not really using the addition of pembro in the CPS less than 1%. This only accounted for about 15% of patients, so the vast majority of HER2-positive patients are going to be PD-L1 positive. The majority of patients treated on the trial were also strongly HER2 positive with IHC 3+. We do see a differential benefit even greater in the patients that are IHC 3+ compared to the 2+ FISH positive.

So I think this is a paradigm-changing trial and very gratifying to see these very high response rates up front, improvements in time on treatment, and overall survival. And of course, now we have the advent of novel later-line HER2-targeted therapies that have also increased our armamentarium to improve treatment for patients.

Dr. Kim:
Yeah. When I first saw the response rate differences, I had hoped for a bigger difference in survival, but I wonder if it's because we now have these very effective second-line and beyond options, like trastuzumab deruxtecan, an ADC, that also seems to have quite impressive response rate, and a survival benefit too. So if it's kind of making up for the fact that, even if a patient hadn't received the

pembrolizumab, they're still able to go on effective therapies later line. So I think overall it's been really gratifying to see what's happening in the HER2 space.

Dr. Ilson:
So now that we have patients that are being on treatment for 8 months, 10 months, 16 months, 2 years, what is your maintenance approach? Because obviously, oxaliplatin has to be discontinued after 4 to 5 months or patients will be getting a fluorinated pyrimidine trastuzumab and pembrolizumab. What is your maintenance approach for patients that seem to be on treatment for longer term?

Dr. Kim:
Yeah. So I definitely stopped the oxaliplatin at 6 months. I keep the 5-FU on as long as tolerated. I find that most of my patients do okay with it. Certainly, I'm open to dose reductions of the 5-FU, but it's hard for me to really let go of the chemotherapy. I think the chemo is very important. And then I think a big discussion is we have these patients, a subset of our patients who have this long-term survival, and some of my patients are approaching the 2-year mark, and do we continue the pembrolizumab? Because there is some data that there doesn't seem to be additional benefit continuing the pembro after 2 years. So I do have a discussion with the patient especially if they're having any immune-related side effects, about potentially dropping the pembrolizumab and continuing with the 5-FU and the trastuzumab. But a lot of it, I think, at that point depends on what their quality of life is, what they would like to do with their time. I try to spread out the infusions a little bit longer too so they have less time in the infusion chair.

Dr. Ilson:
Yeah, we have certainly had flexibility in dosing schedules with both trastuzumab and pembro. And then the option to use oral fluorinated pyrimidine, the maintenance question really has never been clearly addressed. I know in the original ToGA trial, there was permissibility to give trastuzumab alone as a maintenance, but we never heard any follow-up about whether that approach was used or whether it was efficacious. So I, like you do, I tend to continue all the drugs. We don't know what component's really helping patients. And the chemotherapy part of the equation may be critical. Even before the era of targeted agents, we have had patients with durable responses to 5-FU platinum followed by 5-FU maintenance, even without a targeted agent.

Dr. Kim:
And although there isn't a phase 3 clinical trial to answer this question, but what if the tumor is claudin positive and HER2 positive? What are your thoughts about how to approach those patients?

Dr. Ilson:
We don't really know what the efficacy is for zolbetuximab in HER2-positive patients because those patients were excluded, and the trial actually required central review to make sure patients were HER2 negative, so we don't really know. We assume – what's the claudin positivity rate in HER2 positive? Do we see the same efficacy benefits for zolbetuximab in HER2-positive patients?

Of course, when we start combining drug on drug on drug, then we add side effects and toxicities. There is ongoing development of adding checkpoints inhibitors to chemotherapy plus zolbetuximab, but that's still early on in development. That would really be a logical segue given that zolbetuximab is an immune-modulating drug. But we probably aren't going to get an answer to that question because, right now, we have a clear standard first-line care approach in HER2-positive patients, which is dual doublet chemotherapy, trastuzumab, and pembrolizumab first line. And again, in those CPS 1% or higher. If patients are CPS negative, then we probably still would go with chemotherapy plus trastuzumab.

Dr. Kim:
Yeah, it seems like we're increasingly running into that sequencing issue now where we have multiple options in the first line, and then what do we do second line and beyond, so we'll need clinical trials to inform how we approach that.

Well, with that, our time is up. We hope you can apply what you learned today to your practice. Thanks for listening.

Chapter 4

Dr. Ilson:
This is CME on ReachMD and I'm Dr. David Ilson from Memorial Sloan Kettering Cancer Center in New York.

Dr. Kim:
And I'm Sunnie Kim from University of Colorado Cancer Center.

Dr. Ilson:
So today, we're reviewing a case and discussing first-line treatment options for patients with HER2-negative, microsatellite stable, PD-L1-positive, claudin 18.2-positive metastatic gastric GE junction adenocarcinoma. And this is a patient case we're going to talk about who received perioperative immunotherapy on a clinical trial.

Okay, so let's start this discussion. This is a 55-year-old man presenting with fatigue, anemia, epigastric pain, and weight loss. Past history shows adult-onset diabetes, hypertension and elevated cholesterol. Endoscopy shows a proximal gastric mass with a biopsy showing adenocarcinoma that was mismatch repair protein proficient, HER2 negative, PD-L1 positive, and a CAT scan showed the gastric mass with no metastasis. Staging, including endoscopic ultrasound, showed a T3 N1 cancer, and at laparoscopy there was no evidence of metastatic disease.

The patient was enrolled on a clinical trial, KEYNOTE-585, which added pembrolizumab to perioperative chemotherapy. This trial employed perioperative 5-FU cisplatin combined with either placebo or pembrolizumab 3 pre- and 3 postoperative cycles, followed by 11 cycles of adjuvant placebo or pembrolizumab.

The patient enrolled on the trial and his course was complicated by skin rash and hypothyroidism. He did receive pembrolizumab. And at surgical resection, he had removal of a T2 N0 cancer.

Seven months after completion of treatment, he presents with abdominal pain and weight loss. A CAT scan then shows bilobar hepatic metastases and ascites, and a liver biopsy confirms recurrent adenocarcinoma, again testing HER2 negative, PD-L1 positive and CPS 5%. The cancer is mismatch repair protein proficient. But now, this novel biomarker, claudin 18.2, was positive at 80%. His exam is normal. ECOG status is 1. Lab values are normal. Next-generation sequencing, not generally informative. P53 mutation microsatellite stable and HER2 non-amplified.

So now that the patient is 7 months post 5-FU cisplatin and pembrolizumab, now with recurrent disease, what is the optimal chemotherapy and targeted agent for this patient? Should he receive FOLFOX plus pembrolizumab or nivolumab, or should he receive, once it's approved, FOLFOX plus zolbetuximab?

So I want to review just briefly the data for perioperative and checkpoints in gastric cancer. We recently saw publication of KEYNOTE-585 study. This was a trial in local advanced gastric cancers stage 2 or 3 clinically, in which patients received perioperative 5-FU cisplatin, 3 cycles pre and 3 cycles post, with the addition of either pembrolizumab or placebo. Nearly 1,000 patients were randomized on this trial and there were dual co-primary endpoints of event-free and overall survival.

On this trial, a small subset of patients did receive the FLOT regimen. About 20% of patients received FLOT, which was added at the end of the study. So 80% got 5-FU cisplatin, and 20% of the patients received the FLOT regimen as their perioperative chemotherapy.

The trial unfortunately did not meet its endpoint of improved event-free survival. The published data looked at the cisplatin 5-FU cohort and also the combined cohort of cisplatin 5-FU and FLOT. And we can see that in neither of these cohorts, although there was initial separation of event-free survival curves, at the end of the day event-free survival did not achieve statistical significance, so this was a negative trial.

If we look at overall survival data, both for this cisplatin 5-FU cohort and the all-patient cohort treated with cisplatin 5-FU and FLOT, there was no clear survival benefit. As designed, this was a negative trial for adding pembrolizumab to perioperative chemotherapy in the neoadjuvant and adjuvant setting.

Now interesting, however, was an enhancement in pathologic complete response rate. In the cisplatin 5-FU cohort, the complete response rate went from about 2% to 14%, and the FLOT cohort, which I'm showing here graphically, a 7% pathologic CR rate went up to 17%, which was a substantial incremental improvement in response rate. So about a 10% incremental improvement in pathologic complete response rate with the addition of a checkpoint inhibitor to perioperative chemotherapy. But a benefit that did not translate into either an event-free or overall survival benefit.

Recently we saw update of event-free survival in the FLOT cohort where, again, we do see this provocative separation of the curves. But this did not reach statistical significance. And looking at an early readout of the overall survival in the FLOT cohorts, the curves are superimposable and did not show survival benefit. And we do know in our case vignette that the patient received perioperative pembrolizumab added to 5-FU platinum and had recurrent disease at 7 months.

Where does zolbetuximab come in? Claudin 18.2 is an exciting new target in gastric cancer. It's a gap junction protein that's only expressed in the stomach and in gastric adenocarcinomas, and it is overexpressed in the vast majority of gastric adenocarcinomas. Zolbetuximab is a first-in-class monoclonal antibody that targets claudin 18.2, and it's thought to work by an immune-mediated mechanism. It may stimulate antibody-dependent and complement-dependent cytotoxicity. The drug by itself does not appear to have significant activity.

However, there were 2 pivotal trials of zolbetuximab added to first-line chemotherapy in metastatic gastric and GE junction adenocarcinomas. The first was SPOTLIGHT, which was a global, randomized, double-blind, placebo-controlled trial in which patients

had to test positive for claudin 18.2 75% or higher. And then patients were randomized to conventional FOLFOX, which was given on an every-2-week schedule, or zolbetuximab cycled on an every-3-week schedule. The primary endpoint of SPOTLIGHT was progression-free survival.

So progression-free survival by independent review was significantly improved for zolbetuximab over the chemotherapy alone, with a nearly 2-month improvement in progression-free survival with a hazard ratio that was statistically significant. And overall survival was also statistically significantly improved with a nearly 2-and-a-half-month improvement in overall survival combining zolbetuximab with chemotherapy compared to chemotherapy alone.

The secondary endpoint of response rate was similar. There was a more durable response seen in the zolbetuximab-treated patients, so even though there was not a difference in overall response rate, the duration of response and durability of response was higher and again, progression-free and overall survival were improved and met the primary endpoints of the trial.

So the second trial globally for zolbetuximab in claudin-positive metastatic gastric and GE junction adenocarcinomas was GLOW. This was a trial using capecitabine oxaliplatin as the chemotherapy backbone, cycled every 3 weeks in combination with zolbetuximab. And this was also a double-blinded, placebo-controlled, randomized, phase 3 trial.

Here we can see that progression-free survival was significantly improved for the addition of zolbetuximab of about 2 months compared to chemotherapy alone, which was statistically significant. And overall survival was also significantly improved by a little bit more than 2 months, favoring the addition of zolbetuximab to chemotherapy over chemotherapy alone. And what is impressive is that there seems to be a durable tail on the curve in patients that continued treatment.

Similar to the SPOTLIGHT trial, response rates were similar for the control arm versus adding zolbetuximab to chemotherapy, but again the durability and tail on the curve for response duration favored the zolbetuximab arm.

So I think based on these positive global two phase 3 trials, we will likely see imminent approval of zolbetuximab in the first-line treatment of metastatic gastric and GE junction adenocarcinomas and, again, patients that test positive for claudin 18.2 with a positivity rate of 75%.

So I think this is an interesting case. Right now, we're not giving checkpoint inhibitors as part of standard treatment for perioperative chemotherapy. How would you treat this patient?

Dr. Kim:
Yeah. Well, we don't have data here, unfortunately, but 7 months seems short to me. Until we get more data, I would say at least a year of disease response before I'd be wanting to rechallenge the patient with an immune checkpoint inhibitor. So in this case where we have another targetable biomarker, I would go more with the zolbetuximab when re-treating again.

Dr. Ilson:
Yeah, I think I would favor that as well. I mean, the recurrence was rather quick even despite the potential down-staging, and I think this patient has 2 options. We don't know what the interval – we had this old arbitrary cutoff of 6 months. If patients got beyond 6 months without progression on a prior treatment or adjuvant, we could still consider the same drugs as viable options. So this is a sort of a data-free zone here. I think we have the option of a checkpoint inhibitor plus chemotherapy, or, once approved, I would tend to agree that this patient would likely be better served with using a novel targeted agent, very high expression of claudin 18.2. Both the SPOTLIGHT and GLOW trials did permit prior adjuvant therapy but that was administered in a minority of patients.

Could also be a suggestion, patients after gastrectomy or partial may have less nausea and vomiting than patients that still have an intact stomach. And the problem is now, we have to choose. We have an option for a checkpoint inhibitor first line or potentially zolbetuximab in a claudin 18.2-positive patient. We don't have the luxury yet of using these drugs later line. You did make a very important point earlier, that if we start with a patient that tests both positive for PD-L1 and claudin 18.2, if they develop immune-related toxicities from chemotherapy plus a checkpoint inhibitor and we have to stop the checkpoint inhibitor and continue chemotherapy, that might be a consideration for a patient that's strongly claudin 18.2 positive and still getting first-line treatment to introduce zolbetuximab. So that's another, I think, way of looking at the case. But prior checkpoint inhibitor, relatively rapid recurrence of disease, would argue probably going to a novel target here.

And we obviously await the results of MATTERHORN. One of the problems with the KEYNOTE pembrolizumab, a perioperative trial, is it had these dual co-primary endpoints. So you had to get event-free survival improved first before you could analyze overall survival.

And even though early on it seemed very provocative, that event-free survival was trending better, at the end of the day it did not reach statistical significance, and overall survival early looks superimposable. The durvalumab trial, event-free survival is the primary endpoint, and we have to see if that's achieved plus or minus the potential overall survival of the endpoint. Very provocative that you get this 10%,

12% incremental improvement in pathologic complete response, which is, I think, also unprecedented for adding a novel agent to perioperative therapy.

Dr. Kim:
Yeah. And I think that the benefit we're seeing with the event-free survival and response rate, but not seeing it so much in survival, I think it really points to us improving upon our subsequent therapies when patients experience disease recurrence, unfortunately, that we have better options for them than previously.

So I think it's going to be very important in those studies to see what the subsequent therapies are.

Dr. Ilson:
And there may be subsets that benefit. We've yet to hear long-term follow-up on the MSI-high patients or the potential higher CPS patients where there're subsets that there may be some more durable benefit. But we have other negative trials for adjuvant checkpoint inhibitors. We have the Japanese ATTRACTION-5 study where everybody got up-front surgery; everybody got adjuvant chemotherapy. That's an Asian approach, surgery followed by adjuvant chemotherapy, and the randomized trial of with or without a year of nivolumab did not translate into a relapse-free survival benefit in that study. So we, right now, we've got 2 out of 3 trials that have been reported early on that are negative, and we'll have to see whether MATTERHORN, with a different design and using the FLOT regimen in all patients and not just 20%, will translate into a benefit.

Dr. Kim:
Yeah. And I do wonder if the adjuvant immunotherapy may not be as effective as the neoadjuvant approach, where being able to recruit immune cells early on in the disease process may be what's providing benefit. But it's a bit sobering seeing the negative KEYNOTE-585 results. We're hoping the MATTERHORN will be different based on those kind of statistical details, as you mentioned, but we'll have to see and hopefully it will result quite soon.

Dr. Ilson:
Okay. Well, I think that's all the time we have for today. I hope this was educational and informative. And I'd like to thank Dr. Kim for a great discussion, and thanks, all, for listening.

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