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Immunotherapy Advances in Early-Stage Upper GI Cancers: Key Trial Insights

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

Dr. Caudle:
Welcome to *Project Oncology* on ReachMD. I'm your host, Dr. Jennifer Caudle, and joining me to discuss early-stage operable tumors and unmet needs in upper GI cancer is Dr. Ronan Kelly. He serves as Chief of Oncology at Baylor Scott and White Health and as the Director of the Charles A. Sammons Cancer Center at Baylor University Medical Center in Dallas, Texas. Dr. Kelly, it's great to have you with us today.

Dr. Kelly:
Thank you very much. It's great to be here.

Dr. Caudle:
So to start us off, Dr. Kelly, how has the early-stage treatment of upper GI cancers evolved over the past decade? And can you tell us what's driving the shift from chemotherapy alone to immunotherapy-based strategies?

Dr. Kelly:
Looking back over the last number of years—we won't go back too far; we can go back maybe the last 10 years—we've had two real paradigms of care. For esophageal cancer, we've had both squamous and adenocarcinoma. We've had chemoradiation as one therapeutic option, followed by surgery. And then we've also had perioperative chemo given pre- and post-surgical resection, mostly for those gastric cancer patients. And then in the gastroesophageal junction space, doctors could pick whichever option they thought the patient would prefer or tolerate.

But we've really started seeing in the last couple of years that the more chemotherapy you give, the better for these patients. Unfortunately, there's a predisposition to spread even in early-stage disease, and so we feel the more systemic treatment is given, the better—certainly for gastric cancer, and recent data would suggest that would be preferable for gastroesophageal junction cancer.

So if you look back over some of the trials in recent years, we had the FLOT4 study, which was published in 2019. That showed that the 4-drug combination FLOT, which contains 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel, is better than what we considered was the standard prior to that, which was an epirubicin-containing regimen. But the median overall survival was about 50 months in the FLOT regimen versus about 35 months in the older chemotherapy regimen. So FLOT4 really became the new standard of care in gastric.

We also had the CROSS trial, and that was moving back to 2012, which showed that chemoradiation was better than surgery alone, and clearly surgery alone is not optimal for any of these patients. We need to be giving them either chemoradiation or chemotherapy. And in that CROSS regimen, again, the median overall survival was about 50 months. So we now had 50 months for these early-stage tumors as our median overall survival.

Then, most recently in 2025, we had the ESOPEC trial, which tried to see if chemoradiation or perioperative chemo was better. And what we started seeing in that study was the more chemotherapy you would give, the better for these patients. So what we saw was a divergence in results. Certainly for gastric and GE junction patients, we had known that chemotherapy was better, but now, we started seeing for esophageal adenocarcinoma that more chemotherapy is also better as a result of the ESOPEC study.

The million-dollar question is, can patients tolerate higher doses of chemotherapy if they get frailer or older? And then your question was around why we would start adding immunotherapy. Well, the question now is, can we move beyond what cytotoxics was doing or what radiation was doing alone? Could we now add a new modality on top to try to engage the immune microenvironment that may be complementary to what some of the older cytotoxic regimens are doing? And so we've seen two studies, which I'm sure we'll talk about: CheckMate 577 and the MATTERHORN study.

Dr. Caudle:
With that background in mind, let's zero in on some key trial data focusing on these immunotherapy approaches. At ASCO 2025, we saw the final overall survival results from CheckMate 577, which showed that the median overall survival with adjuvant nivolumab was 51.7 months versus 35.3 months for placebo. Additionally, overall survival rates at 3 and 5 years with nivolumab compared to placebo were 57 versus 50 percent and 46 versus 41 percent, respectively. And then the last point I'll mention is that the disease-free survival, distant metastasis-free survival, and progression-free survival on subsequent systemic therapy all favor nivolumab.

So given this data, Dr. Kelly, how should we interpret the differences we're seeing by histology?

Dr. Kelly:
Well, thank you. I had the privilege of presenting this data at the ASCO Annual Meeting. So if you look back at the data, the primary endpoint of this large adjuvant study was disease-free survival. And when we initially presented the data—that happened at ESMO in 2020—we showed a doubling in the median disease-free survival from approximately 11 months to 22 months. And the hazard ratio there was 0.76. Now, at ASCO in 2025, we had 5 years of information, so we showed that doubling in the disease-free survival remained.

If you actually break it down into histology, we even saw tripling in the disease-free survival in esophageal squamous cell carcinoma. That went from 11 months to 34 months. So in total, we saw a 16.4-month improvement in overall survival. That was the first time we'd shown the overall survival data. The medians there were 51.7 months versus, as you said, 35.3 months and 16.4 months; for the 5-year overall survival rate, there was an improvement of 5 to 7 percent.

Unfortunately, it didn't quite meet statistical significance, but there was a challenge in the overall survival interpretation because of the subsequent systemic treatment imbalance. And we looked at the number of patients in the placebo arm that got treatment with subsequent systemic therapy—that was 50 percent—but in the patients that had the nivolumab, it was only 37 percent.

So we did an additional post-doc analysis. We did a 2-stage estimation method to try to account for that confounding effect of subsequent treatment. And when we did that, we did see a statistical significance in overall survival of 38.6 months versus 20.2 months. However, the top-line data showed clinically meaningful improvement at 16.4 months, not quite meeting statistical significance. But when you take the confounding effect of subsequent treatment away, we did see a benefit.

Now, there were some very important subgroups to look at. We didn't see efficacy in patients that had a cold tumor—we would call those combined positive score less than 1 when you're looking at the PD-L1 status. In those patients, there was no real benefit in the CPS less than 1. The hazard ratio there was 1.4. Whereas, if you looked at the majority of patients, or 90 percent approximately, that had CPS greater than 1 in their tumors, the hazard ratio there was 0.79. So we're starting to see now, for the first time, in the CheckMate 577 study that the PD-L1 status does matter.

Now, it's important because, remember, there we were giving adjuvant nivolumab after tri-modality therapy, so you're just giving single-agent immune checkpoint inhibitor, and so you would expect that the PD-L1 status would matter. When we talk about MATTERHORN, we didn't see it mattered, but remember there, they're combining durvalumab with chemotherapy, whereas in CheckMate 577, it's just nivolumab alone.

The other important point to look at is there was no real benefit at the GE junction. The hazard ratio there was 1.14. And in fact, the NCCN had been recommending for gastric and GE junction patients already that we should be using perioperative chemotherapy. So now, we have adjuvant nivolumab as a treatment option in esophageal squamous. And then, some patients with esophageal adenocarcinoma are probably too frail to get the higher-intensity chemotherapy that we'll talk about in a minute. So that's really the take-home.

Esophageal squamous seems to be more sensitive than adenocarcinoma, but we are seeing benefits at the esophageal cancer space, so we really need to try to select our patients. I think CPS is a way that we can do that for adenocarcinomas. I don't think we should be giving patients nivolumab if they've got a cold tumor and their PD-L1 is less than 1 when we look at CPS.

Dr. Caudle:
Now, if we look at the perioperative setting, the MATTERHORN trial found that durvalumab plus FLOT led to significantly better event-

free survival than FLOT alone among patients with resectable gastric or gastroesophageal junction adenocarcinoma at 67.4 versus 58.5 percent, respectively. And in terms of safety, adverse events with a maximum grade of 3 or 4 were reported in 340 participants in the durvalumab group and in 334 patients in the placebo group.

So what do you see as the key implications of this data for patient care?

Dr. Kelly:
Well, remember, it's important for the audience to understand that MATTERHORN was predominantly a gastric cancer study. 68.4 percent were gastric, whereas in the prior study I talked about, it was esophageal cancer. There was no gastric cancer. So they're two very different studies with two very different trial populations, and we can't really compare them head-to-head. But I think this is a very exciting study because as I mentioned, the FLOT regimen had been shown to be the new standard of care for gastric and GE junction cancers, and now we're building on that.

So we previously had a failed study where we looked at pembrolizumab plus chemotherapy. That was called Keynote-585, which really didn't show a benefit. But the authors felt that the 4-drug combination with FLOT may engage the immune microenvironment or may cause more immunogenic death, which would then allow the PD-L1 inhibitor durvalumab to really work well. And that's the hypothesis, but we did see a benefit here, and we now call this regimen D-FLOT for short.

So the D-FLOT regimen, as you said, did see an improvement in the event-free survival. We only have the 2-year event-free survival. It didn't quite meet overall survival benefit, but it's still early and we're going to see. We had the 2-year overall survival rate that didn't quite meet statistical significance there. We're going to wait to see what the 3-year and the 4-year overall survival shows to see if that actually does result in statistical significance. But the primary endpoint, like CheckMate 577, was event-free survival, and in 577, it was disease-free survival. Can you prevent recurrence of the disease? And they did show that they could do that with this particular study.

And in terms of the subsequent treatment, what we showed here was that there wasn't such an imbalance in subsequent treatment. About 23 percent in the durvalumab arm had subsequent treatment and 32 percent in the placebo arm had subsequent treatment. So not quite at the same level where I explained there was a need for confounding for subsequent treatment in this particular study.

But this was a positive trial. I think it's becoming the new standard of care. We showed in this study that there was a pathologic complete response rate of 19.2 percent versus 7.2 percent. Overall, in this study, it was pretty well-tolerated, I would say. But there is a little concern for the real-world population: can these patients tolerate the 4-drug regimen if they're slightly older and if they have more comorbidities? So that's where individual doctors will need to decide.

Some people have suggested that maybe you could dose reduce the FLOT, but we don't have great data on that. In fact, we don't have any data if you dose reduce. I told you that the Keynote-585 study with pembro and chemo was negative. They didn't have such intense chemotherapy regimen in that study. So I think we should be a little bit careful about just saying, 'oh, let's dose reduce everyone.' I think we need to select our patients. I think this is clearly the new standard for a younger, fitter patient that can tolerate the treatment. But in those that are older and frail, you need to consider if they can tolerate this. So the doctors will make their decision now about which therapeutic approach they would choose.

I think for gastric, this is clearly a new standard of care. For gastroesophageal junction, this is clearly a new standard of care. And then when you get to esophageal, you get to decide whether you think the patient can tolerate the higher-intensity chemo, which would probably be the better option. But if they're frail, you could consider chemoradiation followed by surgery if you wanted to make sure they could tolerate the regimens.

Dr. Caudle:
For those of you who are just tuning in, you are listening to *Project Oncology* on ReachMD. I'm your host, Dr. Jennifer Caudle, and I'm speaking with Dr. Ronan Kelly about integrating immunotherapy into early-stage treatment strategies for upper GI cancers.

So, Dr. Kelly, we just talked about recent trial data on immunotherapy approaches, but even with these advances, organ preservation remains an unresolved area, particularly in esophageal squamous cell carcinoma. Why has progress here lagged behind other cancers, and what are the possibilities for checkpoint inhibitors in this context?

Dr. Kelly:
Well, remember, when you talk about organ preservation for operable disease, you're talking about, can you leave the site of origin where the primary arose intact? Now, we've started seeing data in that in rectal cancer, where patients have mismatch repair deficiency or microsatellite instability. But for other tumors, that's not very common.

We know that in gastric esophageal, a proportion of patients can also have mismatch repair deficiency, or MSI-high. We're exploring studies there to do organ preservation. Can you give dual checkpoint inhibitors, which is a very high response rate, approximately 60

percent? Can you preserve the organ? Can you leave it in situ and then observe? But we have limited data on that approach.

For esophageal squamous, we have, in the past, treated with definitive chemoradiation, but many of those have been considered high-risk surgeries or inoperable cancers. We still think that if the patient can have a surgical procedure, they should do that, even in esophageal squamous cell carcinoma.

I showed you the data from CheckMate 577 where we were able to give tri-modality therapy of chemoradiation, followed by surgery, followed by nivolumab. I think that's the standard of care in esophageal squamous cell carcinoma. But for those where the surgeon says it's too difficult to do surgery or this patient's inoperable, then you would do chemoradiation. And we're still waiting on some clinical trial results in that group on whether there's a role for immune checkpoint inhibitors to be added in. We're waiting on that data. It should come pretty soon. I hope that will be positive, but we'll have to wait and see.

But whether you can leave the organ there is challenging at the moment. But we do consider doing that in MSI-high or mismatch repair deficient tumors just because they're so sensitive to immune checkpoint inhibition.

Dr. Caudle:
So another gap relates to biomarkers. How should we be thinking about MSI, PD-L1, or other features when making real-world treatment decisions?

Dr. Kelly:
Well, when you look at answering this question, you have to answer, are you talking about advanced metastatic disease or early-stage operable disease? And I know today we're talking about operable disease. So if you borrow the biomarkers that we routinely test for in gastric cancer in the advanced stage, we now have a few. We have HER2, which is seen in about 15 to 20 percent of the patients. We have PD-L1 expression, and now, we have a new cutoff of CPS greater than 1, which occurs in about 80 percent. We have claudin-18.2, which is approximately 38 percent. And then we have MSI-high or mismatch repair deficiency in 5 to 8 percent, depending on what literature you're reading.

So when we borrow those biomarkers and we move them into operable state, the only real biomarkers we have right now in the operable setting are PD-L1 and MSI-high, or mismatch repair deficiency. We didn't have great data on what the PD-L1 status does in operable disease, but now, as a result of CheckMate 577 and MATTERHORN, we know that approximately 90 percent of our patients will have CPS greater than 1, which is important because that's our new cutoff for whether we can use immune checkpoint inhibitors in the advanced setting. I think that'll be important in the operable setting—certainly for adjuvant nivolumab as there's not really any benefit if you've got a cold tumor and the PD-L1 is CPS less than 1. It's about 10 percent of patients. But the hazard ratio there is 1.4 if they've CPS less than 1, whereas it's 0.79 if they've CPS greater than or equal to 1. So that's important there.

In MATTERHORN, when you combine durvalumab with FLOT, it didn't look like PD-L1 was that important in operable gastric. But again, that’s 4 drugs now with a fifth drug added in. So it doesn't look like it's that important when you're doing combo chemo plus IO. With IO alone, it’s more important.

At the moment, we don't have great data on the role of HER2 in operable gastric or esophageal cancer. We had a study called RTOG 1010. It didn't show any benefits with adding trastuzumab into the treatment paradigms, so we’re still waiting to see what other studies will show us. Of course, we have novel drugs in the advanced setting, like antibody drug conjugates with trastuzumab/deruxtecan. Some of those are moving into early stage, but we have no data yet. So we can't really advise on using HER2 in an operable setting. PD-L1, yes, but only with adjuvant nivolumab, not with durvalumab chemo. MSI-high, yes, we would want to see that because that would lead us to think we should give immune checkpoint inhibitors to these patients, probably even dual IO inhibition to try to really turn on the immune system. And then that last biomarker is something called claudin-18.2. We don't have data in early-stage disease; we just have data in the advanced metastatic setting, so it’s too early to be making any determination about where we could position targeting claudin in early-stage patients. Those studies are coming; we just don't have data yet.

Dr. Caudle:
We've certainly covered a lot today, Dr. Kelly, and I'd like to bring all of this together before we close. What do these trial results and remaining gaps in care mean for treatment sequencing and planning?

Dr. Kelly:
Well, some patients are sensitive to immune checkpoint inhibitors; others are not. I think we need better biomarkers than just PD-L1 CPS score. Unfortunately, it’s a heterogeneous and dynamic biomarker. The score can be changed depending on prior treatments, the site of biopsies, and there's some interpretation challenges there. So it's not a perfect biomarker. We need to do a lot better.

We are looking at all of these big phase 3 studies. We're doing in-depth evaluations to see if we can determine other biomarkers, but

nothing has really become primetime as yet to help us decide on that. The other thing we're really waiting for is the circulating tumor DNA data. Unfortunately, that wasn't taken in CheckMate 577, so we don't have the blood to evaluate, but I know it was taken in the MATTERHORN. That may be important because what we'd need to see is who needs treatment after surgery. We know we're overtreating some patients and we're undertreating some patients. Hopefully, if we look at the biomarker work from MATTERHORN, it may be able to tease out who's at high risk for recurrence and if we can optimize their treatment or who's at low risk and we can just leave them alone and not give them any more chemo or immunotherapy. So that'll be very important: figuring who needs adjuvant therapy in a perioperative setting. And I don't think we've got that data. We've started to see a little bit of that in other tumors, but we need to start seeing this in gastric and GE junction as a result of the MATTERHORN trial, and I'm excited to see what that data will bring.

Dr. Caudle:
As those final insights bring us to the end of today's program, I'd like to thank my guest, Dr. Ronan Kelly, for joining me to discuss the new approaches and clinical data that are shaping the early-stage treatment of upper GI cancers. Dr. Kelly, it was great speaking with you today.

Dr. Kelly:
Thank you very much.

Announcer:
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