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Advancing Biomarker Testing Strategies in Upper GI Cancers: From PD-L1 to FGFR2b

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

**Dr. Turck:**
From MSI and PD-L1 to emerging players like FGFR2b, biomarker testing is transforming how we approach upper GI cancers. But integrating these data into timely treatment planning remains a challenge. So what's the best way to make sense of this evolving landscape?

This is *Project Oncology* on ReachMD, and I'm Dr. Charles Turck. Here with me today to share strategies for biomarker testing in upper GI cancers, like esophageal squamous cell carcinoma, as well as gastric and gastroesophageal junction cancers is Dr. Rutika Mehta. She's an Associate Professor of Medicine and an Attending Physician at Weill Cornell Medicine and New-York Presbyterian Hospital. Dr. Mehta, welcome to the program.

**Dr. Mehta:**
Thank you so much, Dr. Turck. It's great to be here.

**Dr. Turck:**
Well, if we start with some background, Dr. Mehta, how has the role of biomarker testing evolved in upper GI cancers, and why is it no longer enough to rely on histology alone?

**Dr. Mehta:**
That's a great question. It was interesting that until several years ago, we used to just rely on a couple of biomarkers. Especially after the TOGA trial, it was HER2, but then came the advent of checkpoint inhibitors and the use of PD-L1. And most recently, we've also seen MSI-high being a very important predictive marker in upper GI malignancies. Although it's a very small percentage of cases that would be MMR deficient or MSI-high, they do have a significant response to checkpoint inhibitors, either by themselves or in combination with chemotherapy.

We have some other new trials such as SPOTLIGHT and GLOW, which have looked at claudin 18.2-targeting monoclonal antibody as well as some upcoming clinical trials, like FORTITUDE-101 and 102, which are looking at bemarituzumab in combination with chemotherapy plus/minus checkpoint inhibitor. It's becoming like a pie that you're breaking down into multiple pieces and trying to personalize treatment options for patients.

So we're no longer relying on chemotherapy by itself as a treatment option but trying to leverage the use of these biomarkers to give more personalized and precision-based medicine.

**Dr. Turck:**
So then let's zero in on some of these biomarkers one by one, starting with microsatellite instability. Where does MSI testing fit into the clinical workflow, and why is it often considered a reflex test?

**Dr. Mehta:**
I feel MSI-high testing is important not just for metastatic GE junction and gastric adenocarcinomas, but also for locally advanced GE junction and gastric adenocarcinomas. You will now see in the NCCN guidelines that even for the locally advanced tumors, MSI testing

is indicated, and those patients should be treated with checkpoint inhibitors preoperatively.

So I think there's relevance in MSI-high testing, both in locally advanced as well as metastatic GE junction gastric adenocarcinomas.

**Dr. Turck:**
Now, PD-L1 is another core biomarker, but there is often some confusion around the CPS and TPS scoring systems. So with that being said, what should we keep in mind when comparing these two scores, and how can that affect treatment planning?

**Dr. Mehta:**
For the majority of the esophageal squamous cell carcinoma clinical trials, the historic PD-L1 testing had been using TPS scoring—tumor proportion score. But also interestingly, all of these studies have given some exploratory endpoints with CPS testing—CPS scoring system—as well. I know in other malignancies, TPS scoring is being used, but I like to keep things pretty simple. I like to use CPS scoring all throughout. There's also the TAP scoring system for PD-L1, which is now being used for some other checkpoint inhibitors. There is also a good concordance between the TAP scoring and the CPS scoring system.

So, in my opinion, I feel if your pathologist can do a CPS score, be it esophageal squamous cell carcinoma, GE junction, or gastric adenocarcinoma, that should suffice the needs of a clinical oncologist in order to test for PD-L1 scoring.

**Dr. Turck:**
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Rutika Mehta about the current biomarker landscape for esophageal squamous cell carcinoma and gastric and gastroesophageal junction cancers.

So if we continue to examine key biomarkers, Dr. Mehta, how has HER2 testing evolved in upper GI cancers, and what are some nuances we should be aware of with respect to HER2 heterogeneity?

**Dr. Mehta:**
So HER2 was our key biomarker, and the foundation was laid by the TOGA trial with the combination of chemotherapy plus trastuzumab showing overall survival benefit in the HER2-positive patients. Since then, we've had approval for an antibody-drug conjugate as well in the second line and beyond setting. And there are several other key anti-HER2-directed therapies that are being explored, both in the first line and second line and beyond settings.

Having said that, something to consider would be the heterogeneity of HER2 expression. It could be heterogeneity within the tumor itself—if I take a biopsy from the primary site, there could be islands of HER2 positivity and islands of HER2 negativity, which we have to be considerate about. There's also heterogeneity between the primary tumor versus the metastatic site. If the patient had been on anti-HER2 treatment and now has new metastatic disease, there is a possibility that the new metastatic disease might not be HER2 positive.

There is one tricky metastatic site—the bone. I do notice that typically when we biopsy the bone as a metastatic site and look for HER2 expression, the decalcified bone typically does not pick up the HER2 staining really well, so I don't rely that much on the HER2 test results when I'm particularly just biopsying a bony metastatic site.

Other things I would say would be that when patients progress on first-line treatment with an anti-HER2 treatment, I typically will re-biopsy to ensure if they're still HER2-positive because that allows me to understand whether I should challenge them with an antibody-drug conjugate targeted against HER2 or offer a different cocktail of chemotherapy antibody.

And last but not least, there is evolving data about some resistance mutations to enter HER2 therapies that can co-occur with HER2 amplification, so something to watch out for if you're definitely doing liquid biopsies. Those are emerging biomarkers to look out for.

**Dr. Turck:**
Now, claudin 18.2 and FGFR2b are two emerging biomarkers. So would you walk us through what we're learning about them and how that's changing our testing strategies?

**Dr. Mehta:**
Absolutely. So, until recently, we used to have MMR, PD-L1, and HER2 as a reflex testing for all gastroesophageal adenocarcinomas. Now, with the approval of the claudin 18.2 monoclonal antibody, we're also testing our patients for claudin 18.2, so that's become our routine practice.

FGFR2b is still to come. There are two large phase 3 trials that have matured or are about to mature. There has been a press release about FORTITUDE-101. We're waiting to hear about these in some upcoming congresses. But if a FGFR2b monoclonal antibody does show overall survival benefit in the first-line setting, it's likely to become standard practice to check FGFR2b in combination with other biomarkers in the first-line setting.

**Dr. Turck:**
Now, with all of these biomarkers available for us to test, how do you balance integrating them into your practice?

**Dr. Mehta:**
I think the one question that always comes up is, “You're doing so many biomarkers; how do you know that there is enough tissue to do these many biomarkers?” And moreover, there's also this push of doing next generation sequencing. So, there's always the matter of tissue as an issue, and how do you prioritize biomarkers?

I like to follow an algorithm. I like to rely on liquid biopsies as a complementary test to tissue testing, especially if I know for sure that tissue is limited. Then, I use liquid biopsies for MSI testing and sometimes even for ERBB2 amplification to look at that in the liquid biopsies, and then do some of the other tests, like claudin or PD-L1 on tissue, which don't have a complementary ctDNA test.

**Dr. Turck:**
Well, we've certainly covered a lot of ground today, Dr. Mehta, but I have one final question for you. Let's say that a tumor expresses more than one actionable biomarker, like HER2 and PD-L1. What are some best practices for sequencing treatments in that kind of situation?

**Dr. Mehta:**
For HER2/PD-L1, if there’s an overlap, I think the answer has been set forth by KEYNOTE-811. So in those patients, we would treat them with chemotherapy with trastuzumab and pembrolizumab, which is an anti-PD1 antibody.

There are questions now arising as to, “How do you treat patients that are claudin 18.2 positive and PD-L1 positive?” We're hoping to get some answers through another phase 3 trial that is being conducted for that subgroup of patients.

And last but not least, there's also some overlap between HER2and claudin 18.2. That is, again, an unknown space at this time. Maybe some future studies will lay grounds on how to treat those patients who are HER2 positive as well as claudin 18.2 positive. At this point in time, I can only say that they surely will receive anti-HER2-directed treatment in the first-line setting, and if they still remain to be HER2-positive and if they progress on the anti-HER2 treatment first line, then they should potentially be receiving an anti-HER2-directed antibody-drug conjugate in the second-line setting until new data becomes available.

**Dr. Turck:**
With those best practices in mind, I want to thank my guest, Dr. Rutika Mehta, for joining me to share her perspectives on biomarker testing strategies in upper GI cancers.

Dr. Mehta, it was great having you on the program.

**Dr. Mehta:**
Thank you so much for the invitation. It was great being here and sharing all these wonderful thoughts.

**Announcer:**
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