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Emerging Biomarker Landscape in Gastro/Gastroesophageal Cancer

Announcer:
Welcome to ReachMD. This medical industry feature, titled “Emerging Biomarker Landscape in Gastro/Gastroesophageal Cancer,” is sponsored by Amgen. Here’s your host, Dr. Charles Turck.

Dr. Turck:
This is ReachMD, and I’m Dr. Charles Turck. Joining me to share considerations for biomarker screening in gastroesophageal cancer, is Dr. Steven Maron. He’s a gastrointestinal oncologist at Memorial Sloan Kettering Cancer Center in New York.

Dr. Maron, welcome to the program.

Dr. Maron:
Thanks so much for having me!

Dr. Turck:
So let's start with some background on gastroesophageal cancer. Dr. Maron, what can you tell us about the burden of disease?

Dr. Maron:
While the incidence of gastroesophageal cancer is relatively low in the U.S. compared to some other parts of the world, it remains a very significant health issue.[1] In fact, the National Cancer Institute estimates that there will be approximately 27,000 new cases of gastric cancer diagnosed in the U.S. this year, and approximately 11,000 deaths.[2]

And what’s particularly concerning is that around 61 percent of patients with gastric cancer have advanced disease at the time of diagnosis.[2] Early detection of cancer may help improve patient outcomes, but the signs and symptoms of early disease are often difficult to recognize, which can lead to delays in diagnosis and poor survival rates.[3]

Dr. Turck:
So given that early detection is challenging, Dr. Maron, can you touch on the challenges in diagnosing and treating gastric and gastroesophageal cancer?

Dr. Maron:
Certainly. So gastroesophageal cancers are complex and heterogeneous diseases. Although historical classification systems can help inform prognosis and treatment decisions, improving patient outcomes remains challenging—in part due to the considerable tumor heterogeneity.[4,5] And so there’s been a lot of interest in our field in the molecular characterization of gastroesophageal cancer and how this can help inform patient management.[5–7]

And at this time, molecular classification has identified multiple tumor biomarkers, some of which are actionable while others are just emerging. Some key actionable biomarkers include the receptor tyrosine kinase HER2 and immune-related biomarkers such as PD-L1 and MSI-High. Emerging biomarkers like FGFR2b and Claudin18.2, a tight junction protein, are also gaining attention. These biomarkers may provide valuable insights into the tumor biology, and we hope they may help in personalizing treatment plan strategies.[5–7]

Dr. Turck:
And as a quick follow-up to that, can you tell us more about how targeted therapies based on molecular profiling may improve outcomes for patients with gastroesophageal cancer?

Dr. Maron:
Sure. Traditional treatment approaches often follow a "one-size-fits-all" model, which may result in a portion of patients not deriving maximal therapeutic benefit as their molecular profiling may be overlooked. Precision medicine leverages clinical, pathologic, and molecular information to direct an individualized treatment plan.[8]

Testing patients with metastatic gastroesophageal cancer for additional biomarkers may broaden options for a patient's treatment plan. For example, identifying HER2 overexpression can guide the use of HER2-targeted therapies.[9,10]

Dr. Turck:
Now, Dr. Maron, a few moments ago you mentioned the emerging biomarker FGFR2b. Can you explain its role in tumorigenesis?

Dr. Maron:
Of course. FGFR2b belongs to the FGFR family of receptor tyrosine kinases.[11] Alternative splicing of the FGFR2 gene can result in expression of the FGFR2b protein isoform.[12] FGFR2b protein is primarily expressed in epithelial cells and is involved in key biologic processes, such as cell proliferation, migration, and angiogenesis.[11,12] When FGF ligands bind to FGFR2b, they activate multiple downstream signaling pathways, including the PI3K-AKT and RAS-MAPK pathways that are known for their involvement in tumor growth and proliferation, which can then drive the development of gastroesophageal cancer.[12–16]

Dr. Turck:
For those just tuning in, you're listening to ReachMD. I'm Dr. Charles Turck, and today I'm speaking with Dr. Steven Maron about the role of biomarker screening in gastroesophageal cancer. This medical industry feature is sponsored by Amgen.

So now that we've touched on the role of FGFR2b in tumorigenesis, Dr. Maron, how can pathologists detect this biomarker?

Dr. Maron:
Well first, it's important to keep in mind that FGFR2b protein overexpression is distinct from *FGFR2* gene amplification. Gene amplification refers to an increase in the copy number of a specific gene, which leads to protein overexpression.[17] However, protein overexpression means there's an overabundance of a specific protein, which can occur due to various biological processes beyond gene amplification, such as dysregulated protein synthesis and degradation.[18,19]

So theoretically, FGFR2b protein overexpression, which is measured by immunohistochemistry, or IHC, of tissue, may occur independently of *FGFR2* gene amplification, the latter typically assessed using next-generation sequencing of plasma ctDNA or tissue next generation sequencing.[20] In fact, data from a 2021 randomized, double-blind, placebo-controlled, phase two study of 155 patients with metastatic gastroesophageal cancer found that 83 percent of patients had FGFR2b protein overexpression in the absence of *FGFR2* gene amplification.[20] This means that relying solely on gene amplification may not capture all tumors with increased FGFR2b expression.[21]

Dr. Turck:
I see. And what considerations should pathologists take into account when using IHC to evaluate biomarker?

Dr. Maron:
IHC is a routine testing modality used to assess protein expression levels in tissue biopsy samples already. In metastatic gastroesophageal cancer, IHC can be utilized to evaluate the expression of key biomarkers, such as HER2 and PD-L1.[22–24]

IHC results typically have a turnaround time of about one to four days as seen in the real-world PD-L1 data.[25] And IHC assessment provides diagnostic guidance with sensitivity[26] and specificity concordance across assay types.[24]

When using IHC for evaluation of FGFR2b protein overexpression in gastroesophageal cancer, several factors need to be considered though. Due to the heterogeneity of gastroesophageal cancer, FGFR2b overexpression may differ across multiple biopsies and repeat testing should be considered.[27] When evaluating staining, we access both the intensity and percentage of moderate to strong tumor cell membrane staining that is two to three plus by IHC. And it's important to note the extent and pattern of staining.[23,28]

Additionally, FGFR2b overexpression has been more frequently identified in tumors with poorly differentiated and diffuse-type histology. Historical studies have also suggested that patients who have FGFR2b-overexpressed gastric cancer have poor prognosis, but further study is needed to confirm these results.[28]

And lastly, the prevalence of FGFR2b overexpression in gastroesophageal cancer of about 20 to 30 percent, and its potential association with poor prognosis make FGFR2b a target that warrants further investigation.[11,20,28,29]

Dr. Turck:
So, Dr. Maron, what else should clinicians consider for biomarker evaluation when performing diagnostic workup of patients with gastroesophageal cancer?

Dr. Maron:
There are actually several important considerations to optimize biomarker evaluation. First, optimal tissue acquisition is needed to ensure complete and accurate testing. And so effective communication between the clinicians performing the biopsies and pathologists who work up the biopsies may help to obtain sufficient tissue quantity and quality for biomarker testing.[30]

As I mentioned a bit earlier, the NCCN Clinical Practice Guidelines in Oncology, also known as the NCCN Guidelines® recommend performing multiple endoscopic biopsy passes, typically around six to eight forceps biopsies, to provide adequate material for histological and molecular analysis.[31] And tissue acquisition procedures should minimize patient risk while ensuring adequate tissue yield.[30] NCCN Guidelines are refined as often as new data and information become available. Please note, the National Comprehensive Cancer Network® (NCCN®) Content referenced in this session may have updated since the time and date of this original recording.

Second, timely ordering and reporting of test results may be crucial. Pathologists and oncologists can support the development and implementation of reflex panel testing protocols to ensure all appropriate biomarkers are tested, reducing turnaround time for biomarker testing results, and decrease the time to treatment initiation.[32] Additionally, documenting test results in the patient's electronic health record may allow for easier access or retrieval throughout the patient's journey.[30]

Lastly, staying current with rapidly evolving practice standards is important. So clinicians may consider participating in multidisciplinary tumor boards and other formal venues to keep up to date on biomarker testing strategies, evolving guidelines, and sharing best practices.[30]

Dr. Turck:
Well, you've certainly given us a lot to think about, Dr. Maron, but before we wrap up, what final thoughts would you like to leave with our audience?

Dr. Maron:
Yes, we've certainly covered a lot of ground regarding gastroesophageal cancer. And from our discussion, it's clear that these cancers pose significant challenges due to their complexity and late-stage diagnosis.

But we're fortunate to have a growing number of actionable and emerging targets in our armamentarium,[5–7] and ensuring adequate and timely upfront testing to get a comprehensive tumor biomarker profile using methods that can detect both molecular and protein alterations is important.[22,23,32]

So by staying current with evolving guidelines and best practices in biomarker testing, we hope to improve patient outcomes with personalized treatment plan options.[30]

Dr. Turck:
That's a great way to round out our discussion on this topic. And I want to thank my guest, Dr. Steven Maron, for helping us better understand the role of biomarker screening in gastroesophageal cancer. Dr. Maron, it was great speaking with you today.

Dr. Maron:
Likewise, thanks so much for having me.

Announcer:
This medical industry feature was sponsored by Amgen. If you missed any part of this discussion, visit Industry Features on ReachMD.com, where you can Be Part of the Knowledge.

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