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Navigating Treatment Paths: Selection and Sequencing in Biomarker-Driven Combination Regimens for First-Line G/GEJ Cancer Therapy

Announcer:
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Dr. Janjigian:
Good afternoon. My name is Dr. Janjigian. I'm a Medical Oncologist and Chief of GI Oncology Service at Memorial Sloan Kettering Cancer Center. Today, I'm joined by my colleague and a specialist in upper GI cancers, Dr. Samuel Klempner, both of our practices and research focuses have been centered on upper GI tumors, particularly gastric and esophageal cancer. And with the current approvals and constantly evolving landscape for this disease, we took the opportunity to highlight some of our thought processes in how we approach the treatment and diagnosis in biomarker selected population.

So, Sam, thanks so much for joining. Why don't we frame the sort of the opportunities and how we biomarker select and sequence these treatments in the clinic? Tell me just, you know, in a nutshell, how do you characterize that adenocarcinoma? And where do you start? You know, is it an early stage or metastatic disease only? And how do some of these biomarkers influence your treatment selection?

Dr. Klempner:
Yeah, you know, I think both of us started a long time ago in targeted therapies in lung cancer, and that's really been the paradigm for targeted therapies in many solid tumors, where biomarkers really define a biology and a patient population, and those are the best biomarkers that we can exploit therapeutically. And finally, we have some hope for our patients in gastroesophageal cancers, where we're really turning towards biomarkers to inform our therapy, not only in the metastatic disease anymore, but now into the non-metastatic setting, as you alluded to.

So taking a high-level view, I think if we see a new adenocarcinoma of the esophagus, GE junction, or stomach, we first ask ourselves, you know, has the workup been completed? And that workup should include biomarker testing. In the non-metastatic space, MSI is the one that has the most clinical relevance as of right now, although I'll admit our institution does test HER2, PD-L1, and even claudin in the non-metastatic space, although that is probably based on what's coming, not what's in current, but MSI, for sure.

When we move to the metastatic setting, which is unfortunately, the majority of our patients, as you know, we have standard of care biomarkers, which include MSI, HER2, and PD-L1. And several emerging targets which we expect to have in our, you know, toolkit in the near future, including Claudin 18.2. And I think both of our institutions are actually testing for this currently. So really it starts with biomarker testing, I mean staging, of course, and performance status and clinical features and patient decisions. But really, to have a full conversation, we need the biomarker panel.

Dr. Janjigian:
Agreed. And so how do you prioritize? So I can tell you our approach. HER2 is, obviously, is critical, but MSI, as you say, so MMR IHC

is done first, HER2 IHC as well in parallel, and then PD-L1. And increasingly, we're starting to test for Claudin 18.2, certainly a new biomarker, but a critical one, as in the subset population you will see really only claudin in overexpression and that is the patient's lifeline in, you know, HER2 negative and PD-L1 low population.

The way that I prioritize personally is, as you mentioned, MSI is for both early stage and stage IV disease, really defines a unique opportunity. So those patients should be prioritized with immunotherapy. HER2 positivity is the next biomarker of priority to target, which with combination of immune checkpoint inhibitors and HER2-directed therapy is, per KEYNOTE-811. And then, let's you know, there's a draw, right, a sort of a balanced approach for PD-L1-positive versus claudin positive, a risk benefit ratio to each approach. How do you think about it?

Dr. Klempner:
Yeah, I mean, in March of 2024, we don't have zolbetuximab yet, but I think we're all thinking ahead, you know, how are we going to approach this problem when we do have it.

I think our initial two steps is very clear, you know, MMR and HER2, yes, I completely agree. PD-L1, we do test, even though you can technically prescribe and get access to these agents independent of level. But there's clearly a relationship between level of expression and relative benefit to the agents. So I think in the high population, which you may call greater than 5 or greater than 10, whoever you're talking to, we clearly will probably lean towards checkpoint inhibition in those patients. There are also multiple claudin agents coming in later lines of therapy which we have access to in the form of trials currently, ADCs, etc.

I think in the PD-L1, you know, low or negative is where the informed decision-making happens. In the negative patients, I will be reaching for claudin-directed therapies most likely. And then in that mid-range, the 1 to 4, I think it's really going to be a balance of when we're thinking a few steps ahead, you know, we want to expose the patients to as many different types of therapy as possible across their journey, different mechanisms of killing tumor cells, etc. So we have a luxury like you do of hopefully being able to expose patients at different places in their journey. So we will look at our portfolio and say, you know, if we have something later, can we use this drug that we don't have later now, etc? I think it will be quite individualized in that setting. I think there will be a few cases where there's, like, 100% claudin and 3+ everywhere, where maybe I'll lean to it.

Dr. Janjigian:
Right. Yeah. And – or, for example, if a patient has gotten nivolumab in adjuvant setting, for example, in resected high-risk gastroesophageal adenocarcinoma, as we use, post chemo RT and surgery, and then recurred relatively quickly, and is claudin positive, I mean, in that patient, even with high PD-L1 or moderate PD-L1 overexpression, it seemed like claudin inhibitors would be an important consideration.

And one important thing to remember that all of these drugs, you know, have a potential to improve the patient's survival, and so at a minimum, you have to test for the biomarker, so that you can make a decision, as informed decision as possible.

Well, thanks for that summary. I think it seems like we're all on the same page. Thanks for joining.

Dr. Klempner:
Yeah, happy to be here.

Announcer:
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