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Practice Changing Highlights in G/GEJ Cancers: The Latest Data from Chicago

Announcer:
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Dr. Klempner:
Hi, my name is Sam Klempner. I'm a GI Medical Oncologist at Mass General in Boston, and I'm happy to provide some updates from ASCO 2024 annual meeting about biomarker-directed therapy in frontline gastroesophageal adenocarcinomas.

Over the past couple years, the major theme has been selecting patients to achieve the best benefit based on what we know about the tumor, and standard biomarker testing is HER2, PD-L1, and MMR deficiency or microsatellite instability. The newest player onto this recently approved in Japan, is claudin 18.2. And with global approvals expected in the near future, this will be the fourth standard of care biomarker that is essentially required for us to know about all of our patients.

Of course, the practice is driven by data, and at ASCO 2024 we saw updates to some seminal trials. I'll start off with immunotherapy, move to claudin therapy and then talk about HER2 therapy. KEYNOTE-859, which was a very, very large global frontline trial asking about the addition of pembrolizumab on top of standard of care 5-FU platinum chemotherapy. This is a positive study, and the updated results confirm the original findings and support pembrolizumab with chemotherapy as a standard option for our patients. Consistent with original reports, we see the magnitude of benefit increases with higher PD-L1 strata. In the intent to treat, the median overall survival was 13 months for the pembrolizumab-containing arm. If you cut the PD-L1 expression if greater than or equal to 10, that number improves all the way to 16 months in the frontline setting. So again, PD-L1 expression does remain a biomarker for this patient population.

Similarly, we saw 4-year survival data for CheckMate 649. And the overall findings of the trial are hold. What remains interesting is that we're now seeing 4-year survival rates of like 13 to 17% in the nivolumab-containing arm of the trial, depending on PD-L1 strata. And this is wonderful news for patients, but the tail of the curve is leveling out around that level. For chemotherapy, it's more around 8% of patients who are alive at 4 years. And so again, more pieces of data to support the idea of frontline checkpoint inhibitor as a standard of care for patients with HER2-negative gastroesophageal adenocarcinomas.

Moving to claudin 18.2, we saw the final survival data from SPOTLIGHT. Again, SPOTLIGHT was a global trial asking the question about adding zolbetuximab to claudin 18.2-positive patients in combination with standard 5-FU oxaliplatin chemotherapy. The trial was positive at final overall survival. The trial remains positive. Overall survival in the zolbetuximab-containing arm is encouraging, 18.2 months. And so this is one of the longest absolute overall survivals we've seen in trials to date. Supporting, one, the need to test our patients for claudin 18.2 to identify people who may benefit from this. And two, supporting the ultimate approval, which we hope for this drug in the near future.

There are multiple strategies to build on claudin. So we know benefit from immunotherapy. We know benefit from claudin 18. Why not

combine? The TranStar trial showed us that this does look like it can be combined without synergistic toxicities, and the activity remains encouraging. In a smaller frontline cohort, we saw the triplet of chemotherapy, TST-001, and immunotherapy, and the response rate was encouraging, and the durability looks promising, as the PFS and OS have not been reached.

Finally, outcomes for HER2-positive patients are good, thanks to KEYNOTE-811. There is still room to build on this, and we saw a novel ADC RC48 in combination with tislelizumab and chemotherapy in the form of S1. This had a very high biologic activity. The response rate was 95% in about a 47-patient trial. And so if this holds, this is a very active combination, and suggests that other ADCs may ultimately have a role in the frontline and are at least worthy of investigation in the setting of trials.

So we talked about immunotherapy, claudin 18.2, and HER2. Hope this was informative. And thank you for your time.

Announcer:
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