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Biomarker-Directed Approaches for Frontline Treatment of Advanced Gastric/GEJ Cancers: The Evidence

Announcer:
Welcome to CME on ReachMD. This episode is part of our MinuteCE curriculum.

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Dr. Lonardi:
Hi, everybody. This is CME on ReachMD. I'm Dr. Sara Lonardi. In this brief lecture I will review the data supporting biomarker-directed approaches for frontline treatment of advanced gastric and gastroesophageal junction cancer.

As you obviously know, HER2 expression was a driver of treatment choice for a long time, as we used to treat HER2-positive cancer with trastuzumab plus platinum-based doublet and HER2-negative with a platinum-based tablet. Recently, new data emerged from the KEYNOTE-811 trial, investigating the efficacy of pembrolizumab combined with the standard chemotherapy plus trastuzumab in HER2-positive gastric cancer patients. The trial was positive both in progression-free survival and overall survival.

And the gain was higher in 85% of patients having a PD-L1 CPS of 1 or more, where the gain in overall survival, progression-free survival, and response rate was even higher than in the intention-to-treat population. That's why pembrolizumab plus trastuzumab and chemotherapy became the preferred option in HER2-positive gastric cancer first-line treatment.

I talked about PD-L1 CPS as an emerging biomarker, and we know since the last years that it is really important both in HER2-positive and HER2-negative tumors, as when we have a PD-L1 positive, we can add immunotherapy to the standard treatment. This was established in HER2-negative tumors by two trials. The first one was the CheckMate 649 trial investigating nivo plus chemotherapy in first line. The trial was positive, with a gain in overall survival in the subgroup of patients with a PD-L1 CPS of 5 or more. And the other trial, the KEYNOTE-859, were investigating pembrolizumab plus chemotherapy in gastric cancer patients, was positive in the primary endpoint on the intention-to-treat population, but the gain was particularly higher in the PD-L1 CPS of 1 or more. That's why both the two checkpoint inhibitors, nivolumab and pembrolizumab, became the valid option in first-line PD-L1-positive gastric cancer patients

Obviously, we don't have to forget the MSI-high. It remains as a strong biomarker for immunotherapy efficacy. We saw both in late line and in first line, in both with pembrolizumab and with nivolumab, that the benefit of receiving a checkpoint inhibitor, even without any chemotherapy combined, is huge in the population of patients with MSI-high or deficient mismatch repair protein metastatic gastric cancer.

In the last year, we also developed new drugs for new targets, like zolbetuximab for tumors overexpressing claudin 18.2 and bemarituzumab for FGFR2b overexpression.

The first one, zolbetuximab, was demonstrated to give benefit in addition to FOLFOX or CAPOX in two randomized phase 3 trials, the SPOTLIGHT trial and the GLOW trial, both meeting the primary endpoint of a benefit in progression-free survival.

Data on bemarituzumab are still preliminary. They are very promising, and the phase 3 trial FORTITUDE just recently completed

development.

To conclude, in HER2 advanced gastric cancer, pembrolizumab plus trastuzumab and chemotherapy is the preferred first-line treatment for HER2-positive advanced gastric cancer with PD-L1 CPS 1 or more. And new treatments are under investigation, including trastuzumab deruxtecan.

For HER2-negative advanced gastric cancer, pembrolizumab or nivolumab plus chemotherapy are two new first-line options in HER2-negative advanced gastric cancer with PD-L1 CPS positive.

MSI-high or dMMR gastric cancer highly benefit from checkpoint inhibitor and might even not require chemotherapy combination. While zolbetuximab plus chemotherapy is an emerging first-line option in claudin 18.2-positive advanced gastric cancer.

And thank you for your kind attention.

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