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What Is the Current Standard for First-Line Treatment of Metastatic HER2-Positive G/GEJ Cancers?

Announcer:
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Dr. Janjigian:
Hello, my name is Dr. Janjigian. I'm a Medical Oncologist and Chief of GI Oncology Service at Memorial Sloan Kettering Cancer Center in New York City. And today, it's a pleasure to update you on the current standard for first-line treatment of metastatic HER2-positive gastric and gastroesophageal adenocarcinoma.

So, by way of background, we've known that HER2 is an important biomarker and a target in our disease for over a decade. Up to 20 to 30% of tumors are HER2-positive, meaning that they have either protein overexpression or gene amplification, or both. And the ToGA study put the treatment on the map over a decade ago based on median overall survival of 13.8 months and overall response rate of 47% when you add trastuzumab to standard first-line chemotherapy. And since then, this field stalled because we know that unlike breast cancer, in gastric up to 30% of co-expressed other RTKs, such as RAS, PI3 kinase, or EGFR with HER2 and really dual inhibition of HER2 with other HER2 inhibitor was insufficient to overcome intrinsic HER2 resistance. And after the initial ToGA study, we've had multiple negative studies failing to improve outcome over trastuzumab with chemotherapy.

The ToGA study really improved outcome. As you can see here, the survival curves early in sustained separation proving that this combination is important in our disease. And recently KEYNOTE-811, for the first time in over a decade was able to change practice for those patients. This was a large study looking at patients with stage IV metastatic disease irrespective of PD-L1 and HER2-positive tumors looking at IHC 3+, IHC 2+, FISH positive. Patients were receiving chemotherapy with pembrolizumab, trastuzumab, and CAPOX standard therapy or placebo plus trastuzumab and chemotherapy, with dual primary endpoint of overall survival and progression-free survival with secondary response as endpoint and disease control rate.

We were able to get FDA approval for this regimen based on secondary analysis with improvement in overall response rate, and recently presented the primary endpoint of progression-free survival, which affirmed a further and definitive FDA approval. This was data presented for progression-free survival at 38.5 months of follow-up, demonstrating clear benefit for addition of pembrolizumab to placebo with hazard ratio of 0.73, median progression-free survival of 10 months for the pembrolizumab-containing arm, and 8.1 months for placebo arm. This was in HER2-positive unselected by PD-L1.

And if you look in the PD-L1 CPS 1 or greater category, the hazard ratio is similar and the delta in the median is more pronounced with placebo arm 7.3 months compared to pembrolizumab arm of 10.9 months. Really, look at the early and sustained separation of the curve at 36-months follow-up, 18% are still alive, which is a game changer for our disease and is quite promising.

The overall survival data is yet to mature. But so far, compared to the ToGA regimen, actually the comparator arm in KEYNOTE-811 performed better, highlighting the impact of even in the standard population of pembrolizumab.

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So, looking at progression-free survival, the subgroup of patients that did not appear to be benefiting is PD-L1 low patients, CPS less than 1 or PD-L1-negative patients. And right now, we in the clinic in standard practice, we do restrict the use of pembrolizumab in HER2-positive PD-L1 CPS 1 or greater patients, but most of the other patients did benefit. And again, the MSI population is exceedingly rare, there were non-MSI patients, so to have this depth and degree of benefit is quite dramatic. Their responses from this regimen, they are clearly better than the standard of care. And the early overall survival data appears to be promising, although it's not yet definitive, but looking at PD-L1 CPS 1 or greater population, pembrolizumab median OS of 20 months, which is a game changer. And again, as I talked about placebo arm here 15.7 months performing better even than you would expect for the historical ToGA study, highlighting the impact again, even despite that placebo arm, which is quite promising. This is a very well tolerated treatment. The side effect profile was the same across the two arms, except immune-mediated side effects.

So, in summary, the KEYNOTE-811 study after decade of negative studies changed practice, and pembrolizumab is FDA approved in HER2-positive PD-L1 CPS 1 or greater population. So, please test your patients and offer them immune checkpoint blockade in combination with HER2-positive – HER2-targeted therapy in this setting.

Thank you.

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