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Released: 02/05/2024
Valid until: 02/05/2025
Time needed to complete: 42m

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What Is the Evidence Supporting CLDN18.2 Targeting in Frontline Management of G/GEJ Cancers

Announcer:
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Dr. Klempner:
Hello, my name is Sam Klempner. I'm a GI Medical Oncologist at MGH in Boston, and I'm here to talk about the evidence supporting CLDN18.2 targeting in the frontline management of gastric and GE junction adenocarcinomas.

So, as a brief reminder, CLDN18.2 is a common biomarker in gastric and GE junction patients. Among patients screened for the SPOTLIGHT and GLOW phase 3 trials, you see about 4,500 patients screened, and you see the prevalence of CLDN positivity using the cut-point was around 38%. So, a little over a third of all patients were positive for CLDN18.2 overexpression.

There is prior evidence supporting the targeting of CLDN18.2 in overexpressing patients. What's shown here is the previously published FAST trial. So, this was a randomized, phase 2, in which an older chemotherapy backbone, EOX, was combined with zolbetuximab. And you can see the Kaplan-Meier curves suggesting the improvement with the addition of zolbetuximab in progression-free survival. And what's shown here are two different CLDN strata. So, at the higher expression levels, the magnitude of benefit as evidenced by the hazard ratio and numerical improvement in progression-free survival was the greatest. So, this helped define the cut-points that may be used for subsequent phase 3 trials, which I'll now get into.

So, in order to validate that phase 2 observation, two parallel phase 3 trials were designed, and the schemas are shown here, aptly named SPOTLIGHT and GLOW. And you can see that, really, these are examining exactly the same question which is: Does the addition of zolbetuximab on top of standard chemotherapy improve progression-free survival as the primary endpoint and then overall survival as a secondary endpoint? The main differences in these two phase 3 trials is really the chemotherapy backbone, one using FOLFOX and the other using CAPOX. And these are published, and I would refer you to the full publication for details. But here are the primary endpoints.

So, you can see that in SPOTLIGHT, this is the FOLFOX-based therapy, that the addition of zolbetuximab on top of FOLFOX in CLDN-positive patients improved the progression-free survival. This is a statistically significant improvement and met the primary endpoints. So, this was a positive phase 3 trial.

Similarly in GLOW, provide additional validation, again, this is a CAPOX backbone. And here you see again, statistically improved progression-free survival with the addition of zolbetuximab, so another positive phase 3 trial.

The overall updates here are shown for overall survival. And you can see improvements in the secondary endpoint of overall survival in both trials. So, this is really great. We have two parallel phase 3 trials that hit the primary PFS and secondary overall survival endpoints, adding strong level 1 evidence in support of CLDN-directed therapies in CLDN-positive patients.

If you compare this across trials, and I don't have time to speak to all of this, but this is a reference. You can see that the relative

magnitude of benefit is similar to the addition of other biologics such as PD-L1 and HER2, where we see biomarker selection and appropriate patient stratification improves outcomes. And so, this is really consistent with the idea of biomarker-directed therapy as the future for gastric and GE junction adenocarcinomas.

Anytime there's a new drug, we have to understand the adverse events. And the primary class effect of this drug is nausea and vomiting. You can see the increased rates of nausea and vomiting on top of what's expected with chemotherapy in the zolbetuximab-containing arm. These events tend to be relatively early and can be managed with standard antiemetics, IV fluid, and supportive care.

Of course, when we have a tumor-restricted target such as CLDN18.2, it opens up a lot of opportunities for additional targeting strategies. And here I've just highlighted a few including cell therapies such as CAR T, engineered monoclonal antibodies, bispecific antibodies, and antibody drug conjugates, such as CMG901, which was recently presented in the ASCO Plenary Series.

So, the key takeaways. This is really a prevalent biomarker, so again, obligated to test our patients to identify people who may benefit. It's a validated target with two phase 3 trials supporting evidence. This improved progression-free and overall survival in CLDN-positive patients. And it's an exciting future for our patients too, because there are multiple additional strategies being explored, perhaps for later line or additional frontline strategies.

Thank you very much. I hope this was informative.

Announcer:
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