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What Is on the 'HERIZON' in 1L HER2+ Gastroesophageal Adenocarcinoma?

Announcer:
You're listening to *Project Oncology* on ReachMD. This medical industry feature, titled "What Is on the 'HERIZON' in 1L HER2+ Gastroesophageal Adenocarcinoma?" is sponsored by BeOne Medicines.

Here's your host, Dr. Jennifer Caudle.

Dr. Caudle:
Welcome to *Project Oncology* on ReachMD. I'm your host Dr. Jennifer Caudle, and joining me today to discuss the latest positive data for patients with first-line HER2-positive gastroesophageal adenocarcinoma, is Dr. Syma Iqbal. She's a Professor of Clinical Medicine at Keck School of Medicine at the University of Southern California. Dr. Iqbal, we're so glad to have you here.

Dr. Iqbal:
Thank you for inviting me.

Dr. Caudle:
To start us off, Dr. Iqbal, could you walk us through the unmet needs and the current treatment options for patients with 1L HER2-positive gastroesophageal adenocarcinoma?

Dr. Iqbal:
I'd be happy to. Gastroesophageal adenocarcinoma includes a group of malignancies comprised of gastric, esophageal, and gastroesophageal junction adenocarcinomas. About 20 percent of gastroesophageal adenocarcinoma patients have HER2-positive tumors, which is defined as IHC 3+ or IHC 2+ with FISH positivity. The first-line standard-of-care treatment was platinum-based chemotherapy plus the HER2-targeted monoclonal antibody trastuzumab for 10-plus years. The addition of a PD-1 inhibitor pembrolizumab to this combination has shown increased efficacy in patients with gastric gastroesophageal junction cancer whose tumors were PD-L1 greater than or equal to one in the KEYNOTE-811 trial. This combination has since been adopted as standard of care for these patients.

For HER2 positive, PD-L1 negative patients, trastuzumab plus chemotherapy has remained the standard of care. However, with the advancement of treatment by addition of immunotherapy, the median overall survival has been less than two years.

This underscores the urgent need for additional treatment options for these patients.

Dr. Caudle:
That's very helpful, Dr. Iqbal. And with that context in mind, has there been any recent study data readout for 1L HER2-positive gastroesophageal adenocarcinoma patients?

Dr. Iqbal:
Yes! There was a phase 3 study called HERIZON-GEA-01, and the data was recently published in *New England Journal of Medicine*. The study compared first-line zanidatamab plus chemotherapy with and without tislelizumab, versus trastuzumab plus chemotherapy in patients with HER2-positive advanced gastroesophageal adenocarcinoma.

Dr. Caudle:
We'll get into the data from this trial in a moment, but before we do, could you describe zanidatamab and tislelizumab for our learners?

Dr. Iqbal:
Of course. Let's start with zanidatamab.

It's a bispecific anti-HER2 antibody that binds to two different extracellular domains on HER2 in a trans configuration. This biparatopic binding enables zanidatamab to crosslink neighboring HER2 proteins, leading to receptor clustering. It has shown reduced HER2 signaling and increased immune activity in preclinical models. Zanidatamab gained its first FDA approval in 2024 for the treatment of patients with previously treated, unresectable or metastatic HER2+ biliary tract cancer.

Moving onto tislelizumab now, this is a PD-1 antibody that is engineered to minimize Fc-gamma receptor binding on macrophages to limit T cell clearance within the microenvironment. It has shown high binding affinity and near-total blocking activity to PD-1 in preclinical models. In 2024–2025, tislelizumab received FDA approval for 3 upper GI cancer indications: in combination with chemotherapy for 1L ESCC, as monotherapy for 2L ESCC in patients who had not received a prior PD-1 inhibitor, and in combination with chemotherapy for 1L HER2-negative gastric/GE junction cancer.

Preclinical models have demonstrated HER2-directed antibodies enhanced tumor immunogenicity with PD-1 blockade through increased antigen presentation and T-cell activation. This phase 3 study hypothesized the combination of zanidatamab and tislelizumab would further augment antitumor response in HER2-positive gastroesophageal adenocarcinoma.

Dr. Caudle:
Thank you for that. And now, can you walk us through the study design of HERIZON-GEA-01?

Dr. Iqbal:
Sure thing. This trial was a global, randomized, open-label, phase 3 study that enrolled patients with histologically confirmed, unresectable, locally advanced, recurrent or metastatic, HER2-positive (that is HER2 IHC 3+ or IHC 2+/ISH-positive) adenocarcinoma of the stomach, gastroesophageal junction, or esophagus. Patients should have ECOG performance-status of less than or equal to one, with no prior HER2-targeted or checkpoint inhibitors in any setting. These patients were randomized to receive zanidatamab and tislelizumab plus chemotherapy, which we will refer to as the triplet; zanidatamab plus chemotherapy, which we will refer to as the doublet; or trastuzumab plus chemotherapy, we will refer to as the control. The chemotherapies of choice were CAPOX or 5-FU plus cisplatin, and the stratification factors included geographical regions, HER2 status, and ECOG performance status. This study was designed to have dual primary endpoints: progression-free survival and overall survival. Please note patients in the zanidatamab-containing arms received mandatory prophylaxis for infusion-related reactions and diarrhea.

Dr. Caudle:
I've noticed that the control was trastuzumab and chemotherapy without pembrolizumab, which you mentioned is the standard of care for patients with HER2 positive gastroesophageal adenocarcinoma whose tumors are PD-L1 positive. What was the reason for that?

Dr. Iqbal:
Great question. Trastuzumab plus chemotherapy was chosen as the comparator because the trial was designed before the approval of trastuzumab with pembrolizumab and chemotherapy from the KEYNOTE-811 study. I also want to mention that PD-L1 status was not a stratification factor for the HERIZON-GEA-01 study. It was retrospectively assessed using tumor area positivity, or the TAP, score.

I would also like to describe the statistical design of this study. A fixed-sequence hierarchical testing procedure was used to demonstrate the superiority of the zanidatamab-containing groups over trastuzumab-chemotherapy with the following hierarchy: progression-free survival in the triplet then the doublet, followed by overall survival in the triplet then in the doublet. The subsequent testing is triggered when the current analysis meets the statistical significance. When all the primary endpoints are met, then the contribution of tislelizumab will be tested by comparing the OS between Arm C and Arm B.

Dr. Caudle:
For those of you who are just tuning in, you're listening to *Project Oncology* on ReachMD. I'm your host, Dr. Jennifer Caudle and today, I'm speaking with Dr. Syma Iqbal about HERIZON-GEA-01 data for 1L HER2-positive gastroesophageal adenocarcinoma.

Now let's turn to the data on patient demographics and baseline characteristics, Dr. Iqbal.

Dr. Iqbal:
Sure.

Overall, they were fairly balanced across all three arms, and largely representative of the general HER2-positive gastroesophageal adenocarcinoma patient population. Roughly 30 percent of patients were enrolled in Europe/North America. Most patients had HER2 IHC 3+ tumors, and about 60 percent of patients had PD-L1 greater or equal to one percent. Most patients had received capecitabine

plus oxaliplatin.

Dr. Caudle:
Let's take a look at the efficacy data now. Could you walk us through those findings?

Dr. Iqbal:
I'd be happy to. First, I'd like to provide a high-level summary of the top-line data.

At the first interim analysis, the triplet met the dual primary endpoints and demonstrated statistically significant PFS and OS improvement compared to the control arm. The doublet met the PFS endpoint but not the OS endpoint vs. the control arm, with additional analyses planned.

To dive a bit deeper. At the first interim analysis, the median follow-up of time was 25.9 months. The triplet demonstrated significant PFS improvement as compared to the control. The median PFS was 12.4 months vs. 8.1 months, with a hazard ratio of 0.63. The doublet also significantly improved PFS as compared to the control, with a median PFS of 12.4 months vs. 8.1 months and a hazard ratio of 0.65. The 18-month PFS landmark was 43.9% for the triplet, and 38% for the doublet, and 20.9% for the control.

When we look at the prespecified subgroup analyses, such as geographical regions, anatomical subtypes, and PD-L1 status for PFS, the triplet and the doublet regimens demonstrated generally consistent benefits across these subgroups relative to the control arm.

In terms of overall survival analysis, the triplet demonstrated significant prolongation of overall survival as compared to the control. The median OS was 26.4 months vs. 19.2 months with a hazard ratio of 0.72.

Overall survival results were consistent across subgroups, including geographic region, HER2 and PD-L1 status favoring the triplet. Regardless of PD-L1 expression level, the triplet showed an OS improvement compared to the control, which is different from the data shown in KEYNOTE-811, where addition of an anti-PD-1 to trastuzumab and chemotherapy showed benefit only in patients with PD-L1 greater than or equal to one.

And at this first interim analysis, the overall survival for the doublet did not meet the prespecified criteria for significance versus the control. Additional preplanned analyses will look at the OS data for the doublet versus the control as the data mature.

Dr. Caudle:
Thank you, Dr. Iqbal, for that detailed summary. You know, I want to talk for a moment about the PD-L1 scoring method used in this study, TAP, or tumor area positivity. We know the more common PD-L1 scoring method is CPS, or combined positive score. Is there any post-hoc analysis of OS data using CPS from this trial?

Dr. Iqbal:
Yes, additional post-hoc analyses were performed to look at OS data using CPS. And the OS results were almost identical compared with the data using TAP, indicating high concordance between these two PD-L1 scoring methods for HER2 positive gastroesophageal adenocarcinoma.

As a key secondary endpoint, the objective response rate was 71% for the triplet, 70% for the doublet, and 66% for the control arm.

Among confirmed responders, the median duration of response was 20.7 months for the triplet, 14.3 months for the doublet, and 8.3 months for the control. The longest duration of response for the triplet strongly suggests the benefit of adding tislelizumab to the doublet regimen.

Dr. Caudle:
Let's turn now from the efficacy data to the safety data. What can you tell us about the safety profile?

Dr. Iqbal:
For the safety profile, treatment exposure was the longest for the triplet, with a median treatment duration of 43 weeks, and roughly 30 weeks for both the doublet and the control. Adverse events of any grade occurred in most patients in each treatment arm, and adverse events of grade 3 or higher occurred in 83 percent of patients in the triplet, 74 percent in the doublet, and 75 percent in the control. Serious adverse events occurred in 59 percent in the triplet, 49 percent in the doublet, and 42 percent in the control. And for adverse events leading to discontinuation of HER2-targeted therapy, it was 13 percent of patients in the triplet, 11 percent in the doublet, and 6 percent in the control. Treatment-related adverse events leading to death was 2.4 percent in the triplet, 0.3 percent in the doublet, and 1.3 percent in the control. And when we look at the adverse events of special interest, infusion-related reactions of grade 3 or higher occurred in two percent of the triplet and the doublet groups and one percent in the control. Left ventricular dysfunction occurred in nine percent in the triplet, six percent in the doublet, and four percent in the control. And immune-mediated adverse events were reported in 38 percent of the triplet group, and the most common being rash at 14 percent.

Diarrhea was the most common adverse event for grade 3 or higher in all three arms, and the rate was higher in the zanidatamab-containing arms: 25 percent for the triplet and 20 percent for the doublet, as compared to 13 percent for the control. Discontinuation of HER2-targeted therapy due to treatment-related diarrhea occurred in four percent of the triplet, one percent of the doublet, and none for the control. Discontinuation of tislelizumab due to treatment-related diarrhea was two percent in the triplet. Among patients experiencing diarrhea, events generally occurred early in treatment during cycle one, and the median duration of first diarrhea events was 14 days with the triplet, 17 days with the doublet, and 10 days with the control.

I mentioned earlier that in this study, diarrhea prophylaxis with loperamide of 4 mg BID for the first 7 days of cycle 1 was mandated for patients in the zanidatamab containing arms for diarrhea management.

Dr. Caudle:
Well, Dr. Iqbal, we just went over a lot of data. And with all of this in mind, could you give our audience a few key takeaways as we start to wrap up our discussion?

Dr. Iqbal:
Sure, I'd be happy to. HERIZON-GEA-01 was the first phase 3 study in 1L HER2 positive gastroesophageal adenocarcinoma to demonstrate a median PFS greater than one year and a median OS greater than two years. At this first interim analysis, the triplet regimen—zanidatamab plus tislelizumab plus chemotherapy—demonstrated statistically significant PFS and OS benefit over trastuzumab plus chemotherapy, and the benefits were generally observed across key prespecified subgroups, including in patients with and without PD-L1 expression. The duration of response was nearly two years for the responders receiving the triplet regimen. The doublet regimen, of zanidatamab plus chemotherapy, showed a statistically significant PFS improvement, and a trend toward OS significance. The safety profile was consistent with the known profiles of each individual treatment. And diarrhea was the most common adverse event, which generally occurred early and resolved within 3 weeks with treatment.

Dr. Caudle:
Can you share with us if the regimens are FDA approved?

Dr. Iqbal:
Yes, the FDA has approved both the doublet and the triplet regimens.

Specifically, the doublet regimen, zanidatamab plus chemotherapy, is approved in adults for the first line treatment of HER2 positive (defined as IHC3 plus) unresectable, locally advanced or metastatic gastroesophageal adenocarcinoma regardless of PD-L1 expression.

The triplet regimen, tislelizumab plus zanidatamab plus chemotherapy is approved in adults for the first line treatment of HER2 positive (defined as IHC3 plus, or IHC2 plus and ISH positive) unresectable, locally advanced or metastatic gastroesophageal adenocarcinoma regardless of PD-L1 expression levels.

Dr. Caudle:
Well, that's a great way to round out our discussion today. And I'd like to thank my guest, Dr. Syma Iqbal, for helping us better understand the HERIZON-GEA-01 data in 1L HER2-positive gastroesophageal adenocarcinoma.

Dr. Iqbal, it was great speaking with you today.

Dr. Iqbal:
Likewise. Thank you for having me.

Dr. Caudle:
And for ReachMD, I'm your host, Dr. Jennifer Caudle.

Please stay tuned to hear some important safety information.

ANNOUNCER:

INDICATIONS

TEVIMBRA is a programmed death receptor-1 (PD-1) blocking antibody indicated for the treatment of adults with:

- **Gastric, Gastroesophageal Junction, or Esophageal Adenocarcinoma:** In combination with zanidatamab-hrii and fluoropyrimidine- and platinum-containing chemotherapy for first-line treatment of HER2-positive (IHC 3+ or IHC 2+/ISH+) unresectable locally advanced or metastatic gastric, gastroesophageal junction, or esophageal adenocarcinoma.

- **Esophageal Cancer:**
  - In combination with platinum-containing chemotherapy for first-line treatment of unresectable or metastatic esophageal squamous cell carcinoma (ESCC) expressing PD-L1 (≥1), **or**
  - As a single-agent for unresectable or metastatic ESCC after prior systemic chemotherapy that did not include a PD-(L)1 inhibitor.
- **Gastric Cancer:** In combination with fluoropyrimidine- and platinum-containing chemotherapy for first-line treatment of unresectable or metastatic HER2-negative gastric or gastroesophageal junction adenocarcinoma whose tumors express PD-L1 (≥1).

IMPORTANT SAFETY INFORMATION

WARNINGS & PRECAUTIONS

- **Immune-Mediated Adverse Reactions (IMARs):** TEVIMBRA can cause immune-mediated adverse reactions, which may be severe or fatal and can occur in any organ system or tissue. Early identification and management of IMARs are essential to ensure safe use of PD-1/PD-L1 blocking antibodies. IMARs may occur at any time during or after treatment. Monitor for signs and symptoms of IMARs. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. For suspected IMARs, initiate appropriate workup to exclude alternative etiologies. Withhold or permanently discontinue TEVIMBRA based on severity and administer systemic corticosteroids or other immunosuppressants as clinically indicated. The IMARs listed were observed in clinical studies of TEVIMBRA (n=2390) and may not include all possible severe and fatal IMARs.
  - **Pneumonitis:** TEVIMBRA can cause immune-mediated pneumonitis, which can be fatal. Immune-mediated pneumonitis occurred in 4.7% of patients, including Grade 3-4 reactions in 1.7% and fatal events in 0.1%.
  - **Colitis:** TEVIMBRA can cause immune-mediated colitis, which can be fatal. Immune-mediated colitis occurred in 0.8% of patients, including Grade 3 reactions in 0.3%.
  - **Hepatitis:** TEVIMBRA can cause immune-mediated hepatitis, which can be fatal. Immune-mediated hepatitis occurred in 1.3% of patients, including Grade 3-4 reactions in 0.9%.
  - **Endocrinopathies:** TEVIMBRA can cause immune-mediated endocrinopathies, including adrenal insufficiency, hypophysitis/hypopituitarism, thyroid disorders, and type 1 diabetes mellitus. Reported rates included adrenal insufficiency (0.5%; Grade 3-4: 0.24%), hypophysitis/hypopituitarism (0.3%; all Grade 2), thyroiditis (1.0%; Grade 2: 0.5%), hyperthyroidism (4.9%; Grade 3: 0.04%), hypothyroidism (12.5%; Grade 3-4: 0.08%), and diabetes mellitus (0.7%; Grade 3-4: 0.4%).
  - **Nephritis with Renal Dysfunction:** TEVIMBRA can cause immune-mediated nephritis with renal dysfunction, which can be fatal. Immune-mediated nephritis with renal dysfunction occurred in 0.2% of patients, including Grade 3 reactions in 0.04%.
  - **Dermatologic Adverse Reactions:** TEVIMBRA can cause immune-mediated rash or dermatitis, including severe cutaneous adverse reactions. Immune-mediated dermatologic adverse reactions occurred in 13% of patients, including Grade 3-4 reactions in 1.2%; Stevens-Johnson syndrome occurred in 0.04% of patients.
  - **Other Immune-Mediated Adverse Reactions:** Other clinically significant immune-mediated adverse reactions occurred in <1% of patients and may involve cardiac/vascular, neurologic, ocular, gastrointestinal, musculoskeletal/connective tissue, endocrine, hematologic/immune systems (including solid organ transplant rejection), and myocarditis-myositis-myasthenia gravis (or myasthenia-like) overlap syndrome. Severe or fatal cases have been reported for some of these reactions.
- **Infusion-Related Reactions:** TEVIMBRA can cause infusion-related reactions, which may be severe or life-threatening. Infusion-related reactions occurred in 4.7% of patients (Grade ≥3: 0.2%). Monitor patients during infusion; slow the infusion for Grade 1 reactions, interrupt the infusion for Grade 2, and permanently discontinue TEVIMBRA for Grade 3 or higher.
- **Complications of Allogeneic Hematopoietic Stem Cell Transplantation (HSCT):** Fatal and serious complications, including graft-versus-host disease, have occurred in patients who receive allogeneic HSCT before or after treatment with PD-1/PD-L1 blockade. Complications may occur despite intervening therapy between treatment with PD-1/PD-L1 blockade and allogeneic HSCT. Monitor patients closely and intervene promptly.
- **Embryo-Fetal Toxicity:** TEVIMBRA can cause fetal harm and potential fetal death as shown in animal studies. Advise females of reproductive potential of the potential risk to a fetus. Verify pregnancy status prior to initiation of TEVIMBRA. Advise females of reproductive potential to use effective contraception during treatment and for 4 months after the last dose.

ADVERSE REACTIONS

The most common adverse reactions (≥20%), including lab abnormalities were:

- **Gastric, Gastroesophageal Junction, or Esophageal Adenocarcinoma (Combination with zanidatamab-hrii and chemotherapy, 1L):** diarrhea, nausea, anemia, decreased appetite, vomiting, hypokalemia, fatigue, rash, decreased neutrophil count, decreased platelet count, peripheral neuropathy, infusion-related reaction, and increased AST.
- **Esophageal Cancer (Combination with chemotherapy, 1L):** decreased neutrophil count, decreased sodium, increased glucose, anemia, fatigue, decreased appetite, increased AST, decreased potassium, increased serum creatinine, decreased calcium, increased ALT, diarrhea, stomatitis, and vomiting.
- **Esophageal Cancer (Monotherapy, 2L):** increased glucose, decreased hemoglobin, decreased lymphocytes, decreased sodium, decreased albumin, increased alkaline phosphatase, anemia, fatigue, increased AST, musculoskeletal pain, decreased weight, increased ALT, and cough.
- **Gastric Cancer (Combination with chemotherapy, 1L):** nausea, fatigue, decreased appetite, anemia, peripheral sensory neuropathy, vomiting, decreased platelet count, decreased neutrophil count, increased AST, diarrhea, abdominal pain, increased ALT, decreased white blood cell count, decreased weight, and pyrexia.

SPECIFIC POPULATIONS
Lactation: Advise women not to breastfeed during treatment and for 4 months after the last dose.

To report SUSPECTED ADVERSE REACTIONS, contact BeOne Medicines at 1-877-828-5596 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see full Prescribing Information.

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