HOPE FOR STOMACH CANCER
PREVENT. TREAT. LIVE.

BIOMARKER CLAUDIN 18.2 UPDATE!

SUMMARIZING THE 10.18.24 FDA ANNOUNCEMENT

BIOMARKER INFORMATION & STOMACH CANCER RESOURCES:

stomachcancerbiomarkers.org

STOMACH CANCER BIOMARKERS

HOPE FOR STOMACH CANCER PREVENT. TREAT. LIVE.

stocan.org

BIOMARKER CLAUDIN 18.2 UPDATE!
SUMMARIZING THE 10.18.24 FDA ANNOUNCEMENT

THE FDA *announcement*

On October 18, 2024, the FDA approved zolbetuximab for untreated adults with locally advanced unresectable or metastatic HER2- gastric or GEJ cancers whose tumors are claudin (CLDN) 18.2 positive* as determined by an FDA-approved test.

The approval is for first-line treatment in combination with chemotherapy containing a fluoropyrimidine (5-FU or capecitabine) and a platinum (usually oxaliplatin). Astellas' zolbetuximab (Vyloy) is a CLDN18.2-directed monoclonal antibody and is the first CLDN18.2-targeted drug to be approved in the US.

PER THE FDA, THIS TREATMENT IS FOR:

For newly diagnosed or yet untreated adult patients with locally advanced or metastatic gastric or GEJ cancers that have moderate to high levels of the Claudin Biomarker.

**defined as >/=75% of tumor cells demonstrating moderate to strong membranous IHC staining*

BIOMARKER CLAUDIN 18.2 UPDATE!
SUMMARIZING THE 10.18.24 FDA ANNOUNCEMENT

What we know so far.

1. ***THE VENTANA CLDN18 (43-14A) RXDX ASSAY** is the FDA-approved test used to work out if patient tumors have sufficient CLDN18.2 to benefit from zolbetuximab therapy.

   The Assay tests the CLDN18.2 protein signal intensity of cells in a patient tumor sample. Positive and negative cut-offs are as follows:

   - Positive = 75% or more cancer cells have moderate to strong signals (CLDN18.2 expression or protein levels).
   - Negative = No or weak CLDN18.2 expression in cancer cells

2. **CLDN18.2** is made in high enough amounts in a sufficient number of tumor cells to be "positive" in about 38% of locally advanced, unresectable (not removable by surgery) or metastatic gastric/GEJ adenocarcinomas. This means that a patient has a 38% chance of being CLDN18.2-positive and eligible to receive zolbetuximab.

3. **CLDN18.2** is a "tight junction" protein made in the mucous membranes of the normal gastric and GEJ adenocarcinomas.

   - "Tight junctions" are where the membranes of cells that are next to each other join together to form a barrier that 1.) stops molecules from getting through and 2.) stops proteins in the cell membranes from moving around.
   - The mucous membrane lines the insides of the stomach and lubricates and protects it.

4. **THE FDA APPROVAL** of zolbetuximab was based on two Phase III trials: SPOTLIGHT and GLOW.

   The SPOTLIGHT trial tested zolbetuximab with mFOLFOX6 (5-FU, folinic acid, oxaliplatin) chemotherapy, and the GLOW trial tested zolbetuximab with CAPOX (capecitabine, oxaliplatin) chemotherapy. Survival in both trials was better with the addition of zolbetuximab to chemotherapy than chemotherapy without zolbetuximab (a placebo was used in its place).

5. IN JAPAN, zolbetuximab was approved for gastric/GEJ adenocarcinomas in March 2024. Since then, many patients in Japan have received zolbetuximab with chemotherapy. In line with SPOTLIGHT and GLOW trials, side effects include nausea, vomiting, and decreased appetite. Antiemetics (medications against nausea and vomiting) can help individuals deal with these effects.

6. IN JAPAN OVER THE LAST 7 MONTHS, doctors' experience suggests, patients who opt for treatment with zolbetuximab plus chemotherapy in the first line should not worry about being left out of other CLDN18.2-targeted agent trials in the second line or beyond. In fact, quite a few patients have taken part in CLDN18.2-targeted trials even after zolbetuximab plus chemotherapy.

- Zolbetuximab plus chemotherapy sometimes results in lower CLDN18.2 levels—but not usually its complete disappearance. Almost all CLDN18.2- targeted trials enroll patients if they maintain high enough CLDN18.2 levels (are CLDN18.2-positive), and different trials might have different CLDN18.2 cutoff levels to define "positive."

7. IF PATIENTS ARE CURRENTLY RECEIVING CANCER TREATMENT in the first line, adding zolbetuximab to their therapy needs some thought.

- If patients are on chemotherapy alone without disease progression and are CLDN18.2-positive, adding zolbetuximab would be strongly recommended.
- If patients are responding to chemotherapy plus a PD-1 inhibitor, swapping to zolbetuximab is not recommended.
- If patients are on chemotherapy plus a PD-1 inhibitor and experiencing disease progression, switching to zolbetuximab is not recommended because zolbetuximab alone has little activity. Using second-line paclitaxel+ramucirumab or joining a clinical trial of treatment containing another claudin-targeted agent is recommended.

8. IF CLDN18.2 RETESTING WILL BE PERFORMED after zolbetuximab therapy and before joining a trial of another CLDN18.2-targeted agent, this retesting will be done under the trial's research budget. It is unclear whether CLDN18.2 retesting would be currently covered by insurance.

BIOMARKER CLAUDIN 18.2 UPDATE!
SUMMARIZING THE 10.18.24 FDA ANNOUNCEMENT

A NOTE ABOUT PD-L1:

It has been under debate for some time now whether individuals with gastric/GEJ cancers should have PD-L1 CPS cut-offs imposed on them before targeted PD-1/PD-L1 checkpoint inhibitors are prescribed. This is because doctors have generally found great benefit for patients with a high CPS > 10, inconsistent benefits for patients with an intermediate PDL1 CPS 1-10, and consistently no benefit if they have PD-L1 <1*.

The FDA has recently been holding meetings to decide on this issue. However, the cut-offs to be used and when they might be imposed are still uncertain.

THE FINE PRINT:

**Meeting of the Oncologic Drug Advisory Committee. FDA. Sept. 26, 2024. Accessed Sept. 26, 2024. https://tinyurl.com/3j2aufse*

Shitara K, Lordick F, Bang YJ, Enzinger P, Ilson D, Shah MA, Van Cutsem E, Xu RH, Aprile G, Xu J, Chao J, Pazo-Cid R, Kang YK, Yang J, Moran D, Bhattacharya P, Arozullah A, Park JW, Oh M, Ajani JA. Zolbetuximab plus mFOLFOX6 in patients with CLDN18.2-positive, HER2-negative, untreated, locally advanced unresectable or metastatic gastric or gastro-oesophageal junction adenocarcinoma (SPOTLIGHT): a multicentre, randomised, double-blind, phase 3 trial. Lancet. 2023 May 20;401(10389):1655-1668. doi: 10.1016/S0140-6736(23)00620-7. Epub 2023 April 15. Erratum in: Lancet. 2023 Jul 22;402(10398):290. doi: 10.1016/S0140- 6736(23)01481-2. Erratum in: Lancet. 2024 Jan 6;403(10421):30. doi: 10.1016/S0140-6736(23)02762-9. PMID: 37068504.

Shah MA, Shitara K, Ajani JA, Bang YJ, Enzinger P, Ilson D, Lordick F, Van Cutsem E, Gallego Plazas J, Huang J, Shen L, Oh SC, Sunpaweravong P, Soo Hoo HF, Turk HM, Oh M, Park JW, Moran D, Bhattacharya P, Arozullah A, Xu RH. Zolbetuximab plus CAPOX in CLDN18.2-positive gastric or gastroesophageal junction adenocarcinoma: the randomized, phase 3 GLOW trial. Nat Med. 2023 Aug;29(8):2133-2141. doi: 10.1038/s41591-023-02465-7. Epub 2023 July 31. PMID: 37524953; PMCID: PMC10427418.

HOPE FOR STOMACH CANCER IS COMMITTED TO SHARING INFORMATION AS IT IS RELEASED. PLEASE CONTACT US WITH ANY QUESTIONS.