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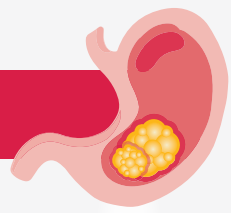
BIOMARKERS IN GASTRIC CANCER



What Are Biomarkers?

Biological molecules found within the blood, fluids, or tissues of the body that indicate a normal or abnormal process, or a condition/disease, such as cancer. There are a wide variety of biomarkers, which can include *proteins, nucleic acids, antibodies and peptides*.[1]

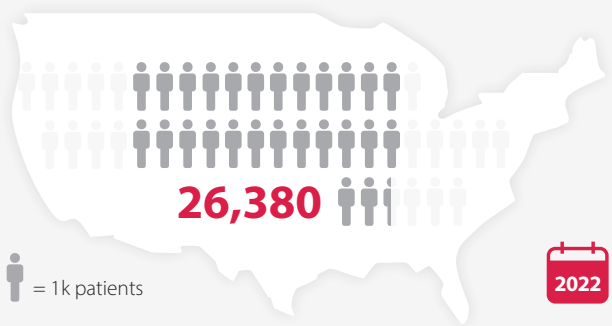
In oncology, biomarkers can **guide treatment decisions** or inform and predict clinical outcomes.[2]

Biomarker testing is a way to look for *genes, proteins, and other tumor markers* that can provide information about the **individual makeup of a person's cancer**, leading to more personalized plans to target eradicating the cancer.[3]

What Are the Unmet Needs in Metastatic Gastric/GEJ Cancer?

Gastric cancer is the **fifth most common cancer globally**, with more than one million cases diagnosed in 2020.[4]

In the U.S., about **26,380** new cases of stomach cancer* are expected to be diagnosed in **2022**.[5]



Stomach cancer and gastric cancer are often used interchangeably.

How Can Biomarkers Be Applied In Treating Gastric Cancer?

Established biomarkers are currently used to create more specific molecular profiles in tumors and inform clinical decisions.

Emerging biomarkers are expanding our view of patient populations and biomarker testing could provide a more comprehensive patient profile.

As novel biomarkers emerge, they may reveal more opportunities to advance care for metastatic gastric/GEJ cancer.

What Are Types of Established Biomarkers in Gastric Cancer?

PD-L1

- Defined as a protein that acts as a "brake" to keep the body's immune responses under control. When it binds to another protein PD-1 found on T cells, it puts the brakes on cells and enables survival of the tumor cells. Targeted PD-L1 therapies look to release the brakes on the immune system and enable T cells to kill tumors cells. [6]
- PD-L1 expression has been detected in various tumors, including *lung, colon, ovarian and gastric cancers*.[7]
- Prevalence of PD-L1 has been reported for several positivity thresholds throughout various studies in gastric/GEJ cancer. **67-73%** CPS >1, **29-31%** CPS >5, and **16-18%** CPS >10. The level of PD-L1 expression can vary across tumor types and throughout the body.[8,9]

HER2 (positive)

- HER2 is a protein in normal cell growth, but can be found in larger amounts in certain types of cancers causing cancer cells to grow at a more rapid rate.[10]
- Studies have shown HER2 overexpression is present in several cancers, including *colorectal, breast, ovarian, prostate, lung, gastric and gastroesophageal cancers*.[11]
- HER2 positivity has been reported in **22%** of advanced metastatic/GEJ cancers.[12]

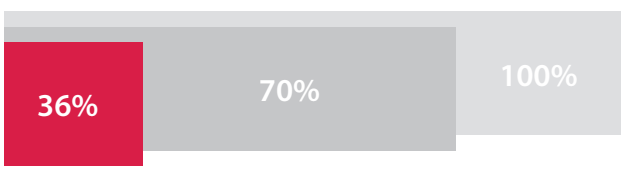
MSI/dMMR

- Microsatellites are short, repeated sequences of DNA. Microsatellite instability (MSI)-high cancer cells may have a defect in the ability to correct mistakes that occur when DNA is copied in the cell.[13]
- MSI is most often found in *colorectal cancer, gastric cancer and endometrial cancer*.[14]
- High MSI/dMMR expression has been reported in **4%** of metastatic gastric/GEJ cancers.[15]

What are Types of Emerging Biomarkers?

Claudin 18.2 (CLDN18.2)

- CLDN18.2 is a member of the claudin family of proteins. Claudins are a major component of tight junctions, which are intercellular spaces between cells that regulate the flow of molecules between such cells.[16-18]
- Pre-clinical studies have shown that CLDN18.2 may become more exposed and accessible to antibodies **as gastric tumors develop**.[16,19,20]
- While **approximately 70%** of metastatic GC/GEJ cancers express CLDN18.2 at any level, recent studies have shown that **approximately 36%** of these cancers meet the qualification of being CLDN18.2 positive, or having a high expression (2+/3+ staining in >75% of tumor cells).[21]



FGFR2b

- Fibroblast growth factor receptor (FGFR2) is a gene that creates a protein that is active in cell division and creation, as well as the formation of new *blood vessels, wound healing, and bone growth and development*.[22]
- A FGFR2 mutation can cause these proteins to be overactive causing certain cancers and genetic conditions.[22]
  - –The FGFR2 receptor undergoes a mechanism in which it is modified and rearranged resulting in a variant called FGFR2b.[23]
- Studies have shown that FGFR2b overexpression can be observed in **30% of gastric/GEJ cancers**.[22,23]

How Can Biomarkers Be Tested For?

Initial diagnostic panels that include biomarker testing can help map the path forward for patients and lead to more informed clinical decisions.[24]

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) recommend:[24]

- Testing for all established biomarkers (HER2, PD-L1 and MSI) when a patient is initially diagnosed and/or if metastatic disease is confirmed or suspected.
  - –PDL-1 testing may be considered in patients who have locally advanced, recurrent, or mGC in those who are candidates for treatment with PD-1 inhibitors.
  - –MSI testing should be done on all newly diagnosed GC patients.
- The use of additional testing (IHC/FISH/targeted PCR) should be considered first, followed by additional NGS testing.

Additional tests for emerging biomarkers are currently under investigation.

[1]Henry NL and Hayes DF. Cancer biomarkers. Mol Oncol 2012;6(2):140-6.

[2]Parker JL, Kuzulugil SS, Pereverzev K, et al. Does biomarker use in oncology improve clinical trial failure risk? A large-scale analysis. Cancer Med 2021;10(6):1955-63.

[3]National Cancer Institute. Biomarker testing for cancer treatment (12-14-2021). https://www.cancer.gov/about-cancer/treatment/types/biomarker-testing-cancer-treatment. Accessed 02-03-2022.

[4]Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021;71(3):209-49.

[5]American Cancer Society. Cancer Facts & Figures 2022. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2022/2022-cancer-facts-and-figures.pdf. Accessed 01-12-2022.

[6]National Cancer Institute. NCI dictionary of cancer terms: PD-L1. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/pd-l1. Accessed 05-20-2022.

[7] Qing Y, Li Q, Ren T, et al. Upregulation of PD-L1 and APE1 is associated with tumorigenesis and poor prognosis of gastric cancer. Drug Des Devel Ther 2015;9:901-9.

[8]Schoemig-Markiefka B, Eschbach J, Scheel AH, et al. Optimized PD-L1 scoring of gastric cancer. Gastric Cancer 2021;24(5):1115-22.

[9]Fuchs CS, Özgüroğlu M, Bang YJ, et al. Pembrolizumab versus paclitaxel for previously treated PD-L1-positive advanced gastric or gastroesophageal junction cancer: 2-year update of the randomized phase 3 KEYNOTE-061 trial. Gastric Cancer (Epub) 09-01-2021.

[10]National Cancer Institute. NCI dictionary of cancer terms: HER2. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/her2/. Accessed 03-10-2022.

[11]Abrahao-Machado LF, Scapulatempo-Neto C. HER2 testing in gastric cancer: an update. World J Gastroenterol 2016;22(19):4619-25.

[12]Van Cutsem E, Bang YJ, Feng-Yi F, et al. HER2 screening data from ToGA: targeting HER2 in gastric and gastroesophageal junction cancer. Gastric Cancer 2015;18(3):476-84.

[13]National Cancer Institute. NCI dictionary of cancer terms: microsatellite instability. https://www.cancer.gov/publications/dictionaries/cancer-terms/search/microsatellite%20instability/?searchMode=Begins. Accessed 07-23-2021.

[14]Baudrin LG, Deleuze JF, How-Kit A. Molecular and computational methods for the detection of microsatellite instability in cancer. Front Oncol (Epub) 12-12-2018.

[15]Fuchs CS, Doi T, Jang RW, et al. Safety and efficacy of pembrolizumab monotherapy in patients with previously treated advanced gastric and gastroesophageal junction cancer: phase 2 clinical KEYNOTE-059 trial. JAMA Oncol 2018;4(5):e180013. Erratum in: JAMA Oncol 2019;5(4):579.

[16]Niimi T, Nagashima K, Ward JM, et al. Claudin-18, a novel downstream target gene for the T/EBP/NKX2.1 homeodomain transcription factor, encodes lung- and stomach-specific isoforms through alternative splicing. Mol Cell Biol 2001;21(21):7380-90.

[17]Sahin U, Koslowski M, Dhaene K, et al. Claudin-18 splice variant 2 is a pan-cancer target suitable for therapeutic antibody development. Clin Cancer Res 2008;14(23):7624-34.

[18]Coati I, Lotz G, Fanelli GN, et al. Claudin-18 expression in oesophagogastric adenocarcinomas: a tissue microarray study of 523 molecularly profiled cases. Br J Cancer 2019;121(3):257-63.

[19]Türeci O, Sahin U, Schulze-Bergkamen H, et al. A multicentre, phase IIa study of zolbetuximab as a single agent in patients with recurrent or refractory advanced adenocarcinoma of the stomach or lower oesophagus: the MONO study. Ann Oncol 2019;30(9):1487-95.

[20]Rohde C, Yamaguchi R, Mukhina S, Sahin U, Itoh K, Türeci Ö. Comparison of Claudin 18.2 expression in primary tumors and lymph nodes metastases in Japanese patients with gastric adenocarcinoma. Jpn J Clin Oncol 2019;49(9):870-6.

[21]Pellino A, Brignola S, Riello E, et al. Association of CLDN18 protein expression with clinicopathological features and prognosis in advanced gastric and gastroesophageal junction adenocarcinomas. J Pers Med (Epub) 10-26-2021.

[22]National Cancer Institute. NCI dictionary of cancer terms: FGFR2 gene. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/fgfr2-gene. Accessed 03-10-2022.

[23]Ooki A, Yamaguchi K. The beginning of the era of precision medicine for gastric cancer with fibroblast growth factor receptor 2 aberration. Gastric Cancer 2021;24(6):1169-83.

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