STOMACHCANCERBIOMARKERS.ORG

STOMACH CANCER
BIOMARKER-GUIDED TREATMENTS

Cancer **BIOMARKERS** are usually genes (pieces of DNA inside a cell) or proteins (made from genes) that have changes or errors in them. They can act as targets for therapy or predict response to immunotherapy.

EMERGING BIOMARKERS are filling in the gaps about how biomarkers can be tested and used in cancer care. Researchers are trying to fill those gaps using lab studies and clinical trials. New biomarkers and treatments are worth keeping an eye on and might be tested if you decide to enroll in a clinical trial.

If you have **LOCALLY ADVANCED, ADVANCED UNRESECTABLE, OR METASTATIC STOMACH CANCER**— you should get tested at the time of diagnosis and again at long-term treatment crossroads.

TESTING is usually done via cancerous tissue samples. Additional factors, such as how your cancer behaves and how your body responds to a treatment, can influence how successful that treatment is.

4 WAYS to collect samples:
1. EDG Biopsy
2. Core Needle Biopsy, CT guided
3. Core Needle Biopsy,Ultrasound-Guided
4. Surgical Resection

The table below is applicable to you mainly if you have cancer that cannot be surgically removed or is metastatic. If you have locally advanced disease that may be surgically removed, the standard treatment options are surgery alone, surgery with chemotherapy before and/or after it, or surgery with chemotherapy plus radiation therapy before or after it. Nivolumab may also be helpful but is not yet dependent on biomarker status. If your tumor is MMRd/MSI-H (see below) then surgery alone without chemo or radiation therapy could be the best option for you.

BIOMARKER	WHAT IS IT?	HOW MIGHT YOU BE TREATED?
HER2	• A protein involved in normal cell growth. • HER2 positive = cancer cells can have larger than normal amounts of HER2. • 10-15% of Gastric cancer are HER2 positive. *Note: HER2 may also be called c-erbB-2, HER2/neu, and human epidermal growth factor (EGF) receptor 2.*	**If your tumor has normal cell levels of HER2** (is HER2 negative), your first treatment regimen will involve standard chemotherapy plus nivolumab (Opdivo), depending on the PD-L1 CPS and your other treatment options. **If your tumor is HER2 positive,** you might be treated with a targeted therapy called trastuzumab (Herceptin®) plus standard chemotherapy and other therapy such as pembrolizumab (Keytruda) in line with your health and other biomarker information. In later lines, you might receive trastuzumab deruxtecan (Enhertu®) if you already received trastuzumab in the first line. Other standard later line chemotherapy and targeted therapies are also options for HER2 positive cancers.
PD-L1	• The PD-L1 protein on tissue cells naturally binds to PD-1 on T cells (the immune system), putting the brakes on our immune response to these cells. The amount of PD-L1 on a cancer cell (its PD-L1 positivity) can be scored by a combined positivity score (CPS) of both tumor cells and infiltrating immune cells, and ranked as greater than or equal to 1 (>1), >5, or >10 or less than 1 (<1) • Generally, CPS>5 or CPS >10 is necessary to derive significant benefit from anti-PD-1 therapies. The higher the level, the more likely there will be benefit. • The incidence of CPS>10 is around 15-30% of gastric cancers • The incidence of CPS>5 is around 30-60% of gastric cancers.	**If your tumor is HER2 negative and has a PD-L1 score CPS>5,** you should receive nivolumab combined with standard. If you have a score of CPS<5, this may still be an option and should be discussed with your doctor, for example if your tumor is MSI-H. **If your tumor is HER2 positive and has a PD-L1 score CPS>10,** you should receive pembrolizumab combined with trastuzumab and standard therapy. If you have a score of CPS<10, this may still be an option and should be discussed with your doctor.

STOMACH CANCER

BIOMARKER-GUIDED TREATMENTS (continued)

BIOMARKER	WHAT IS IT?	HOW MIGHT YOU BE TREATED?
MSI-H/ MSS/ MMRd	• Microsatellites are short, repeated strings of DNA. • MSS is microsatellite stability, whereas MSI-High (MSI-H) is microsatellite instability-high. • Microsatellite instability is a consequence of loss or deficiency of DNA mismatch repair (dMMR) protein function, where cells cannot easily repair certain genetic mistakes in the DNA. • In MSS, cells carry out DNA repair normally or proficiently (pMMR). In MSI-H, there are lots of mistakes leading to microsatellite instability and also many mutations in the DNA (called hypermutation or high tumor mutation burden TMB-high). • MSI-H occurs in ~3% of locally advanced or advanced metastatic gastric cancers.	**If your tumor is MSS,** you will be treated with standard chemotherapy and other therapy in line with your health and other biomarker information.. **If you have an MSI-H tumor,** you should receive a checkpoint inhibitor with either nivolumab or pembrolizumab, with or without standard chemotherapy and other therapy in line with your health and other biomarker information. In the second line, pembrolizumab or dostarlimab-gxly may be useful if you did not receive immunotherapy in the first line for whatever reason. **If surgical removal of your tumor is an option, and your tumor is mismatch repair protein deficienct (MMRd),** then surgery alone without chemotherapy or radiation could be the best option and should be discussed with your doctor.
NTRK fusion	A piece of the NTRK gene joins with another piece of gene and leads to abnormal TRK proteins that can cause cancer cells to grow. This occurs in <1% of patients.	If your tumor did not respond to initial therapy and has an NTRK fusion, treatment with NTRK inhibitors entrectinib or larotrectinib is a good option.
TMB	• Tumor mutational burden (TMB) that measures the total number of gene mutations in a tumor sample - reported as “mutations per megabase” or “mut/Mb”. • TMB-high is greater than or the same as 10 mut/Mb) • MSI-H tumors are usually TMB-H, but sometimes MSS tumors can also be TMB-H.	• There is some suggestion that the higher the TMB score, the higher the chance that immunotherapy checkpoint inhibitors will be effective. You might be treated with a checkpoint inhibitor with or without standard chemotherapy and other therapy in line with your health and other biomarker information. • If you are about to be treated in the second line and your tumor is TMB-high, pembrolizumab treatment is an option if you have not received immunotherapy in the first line for whatever reason.
BRAF V600E	• BRAF V600E is a mutation (change) in the BRAF gene. • The BRAF gene codes for a protein called B-Raf which manages cell growth. • The BRAF V600E mutation stops the B-Raf protein from working correctly and causes cells to divide nonstop, making normal cells become cancerous. • The BRAF V600E mutation exists in just over 0.2% of gastric cancers. • B-Raf protein is part of a larger chain of events called the RAS-RAF-MEK-ERK pathway, which helps control how cells grow, multiply, and survive.	If you have gastric cancer with a BRAF V600E mutation and you have already received initial therapy, your doctor may recommend the use of a BRAF inhibitor (dabrafenib) in the second line, together with another drug, a MEK inhibitor (trametinib), to do a double-whammy on the RAS-RAF-MEK-ERK pathway and stop the out of control growth.
RET fusion	• A piece of the RET gene joins with another piece of gene, which leads to abnormal RET proteins. This occurs in <1% of patients. • The RET protein normally helps prevent cancers. A RET gene fusion (FYOO-zhun) causes the protein to stop working as it should, and cancers grow.	If you have gastric cancer with a RET gene fusion and you have already received initial therapy, your doctor may recommend the use of a RET inhibitor selpercatinib in the second line.

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EMERGING BIOMARKER-GUIDED TREATMENTS (continued)

EMERGING BIOMARKER	WHAT IS IT?	HOW MIGHT YOU BE TREATED IF THIS BIOMARKER TESTING AND TREATMENT BECOMES STANDARD, WHEN IT IS FDA APPROVED?
Claudin 18.2 (CLDN18.2)	• This protein is found in the moist protective stomach lining (mucosa) and is found between the mucosal cells (called tight junctions). Around 35% of metastatic gastric/GEJ cancers produce this protein in large quantities (called CLDN18.2 positive or overexpressing). • **Negative** = the cancer cells have a normal cell's amount of CLDN18.2. • **Positive** = the cancer cells make CLDN18.2in larger than normal quantities • Zolbetuximab inhibited CLDN18.2 in 2 Phase III (late stage) clinical trials called SPOTLIGHT and GLOW. The FDA granted priority review to zolbetuximab in July 2023. At the beginning of January 2024, it was reported that the approval of zolbetuximab had been delayed for a couple of months while a review of the agent's manufacturing processes was carried out. There is no concern about clinical safety or efficacy.	If your tumor is CLDN18.2 positive and HER2 negative, your first treatment regimen could involve standard chemotherapy plus zolbetuximab. If your tumor is CLDN18.2 positive, HER2 negative, and PD-L1 CPS<5 or <10 (i.e. PD-L1 negative), then this would be a good option. If your tumor is PD-L1 CPS≥5 or ≥10 (i.e. PD-L1 positive) and CLDN18.2 positive, then you would have either nivolumab or zolbetuximab as options added to standard chemotherapy. Zolbetuximab combined with other targeted therapies such as trastuzumab or nivolumab/pembrolizumab are yet to be approved or investigated in large phase 3 studies to date.
FGFR2b	• FGFR2b is an unusual form of fibroblast growth factor receptor 2 (FGFR2). • Being FGFR2b positive means having high amounts of FGFR2b and unusually high cell growth and blood vessel formation (angiogenesis), which contribute to cancer progression. • Bemarituzumab is an antibody against FGFR2b. • Around 80%-85% of patients with advanced gastric/GEJ cancers are HER2-negative, and about 30% of these patients are FGFR2b-positive. In these 30% HER2-negative/FGFR2b positive patients, bemarituzumab was beneficial in a phase a 2 clinical trial. • Two Phase 3 trials are ongoing: One study is evaluating FOLFOX with or without Bemarituzmab, and another study is evaluating FOLFOX plus nivolumab with or without Bemarituzmab.	If phase 3 study results are favorable and if your tumor is FGFR2b positive and HER2 negative, your first treatment regimen could involve standard chemotherapy plus bemarituzumab. Bemarituzumab combined with other targeted therapies such as trastuzumab, nivolumab/pembrolizumab, or zolbetuximab are yet to be approved or investigated in large phase 3 studies.
LINE-1 ORF1p	The Long INterspersed Element-1 Open Reading Frame 1 protein (LINE-1 ORF1p) is a highly specific biomarker that is widely expressed in many cancers.	Studies of this biomarker in blood have shown that it can be used for diagnosis, prognosis, and therapeutic response monitoring in gastroesophageal cancers. In a group of patients treated with a range of systemic therapies, pretreatment plasma ORF1p levels were higher in non-responders than responders, with no exception. After treatment, non-responders still had detectable biomarker levels, whereas in responders, the levels became undetectable. LINE-1 ORF1p could be highly useful as a treatment biomarker in the clinic.[1]

** Referenced from NCCN Guidelines on Stomach Cancer**

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