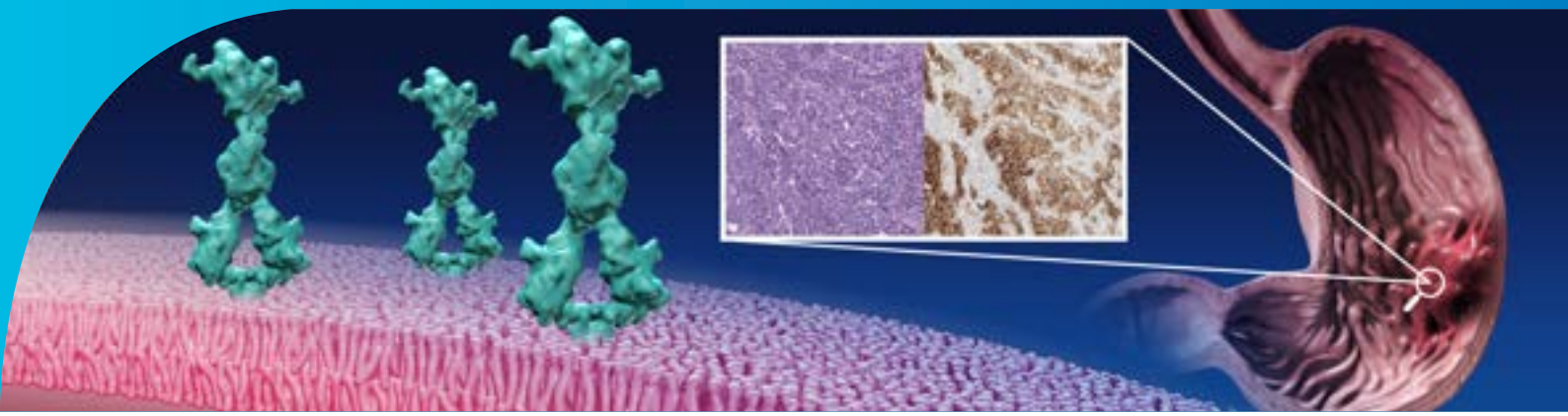
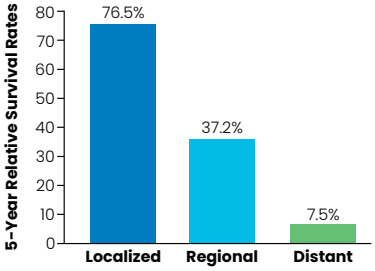
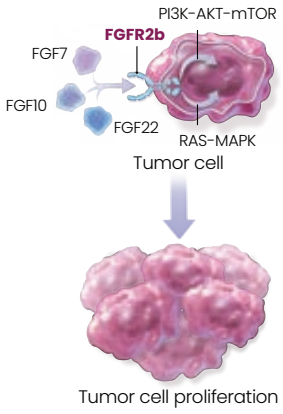
FGFR2b—An Emerging Biomarker and Investigational Target in Advanced Gastric/GEJ Cancer



5-Year Relative US Survival Rates by Stage of Diagnosis From 2015-2021[1]





GASTRIC CANCER IS THE FIFTH MOST COMMON CANCER AND THE FIFTH LEADING CAUSE OF CANCER-RELATED DEATH WORLDWIDE[2,*]

60% of patients with gastric cancer present with advanced-stage disease† at the time of diagnosis in the US.[1]

The 5-year relative survival rate for patients with gastric cancer that includes distant metastasis at diagnosis is only 7.5% in the US.[1]

*Source: Global Cancer Statistics 2022. †This includes patients with regional disease, or those whose cancer has spread to regional lymph nodes, and metastatic disease at the time of diagnosis. There were 30,300 estimated new cases in 2025.[1]

OVEREXPRESSION OF FGFR2b PROTEIN DRIVES TUMORIGENESIS

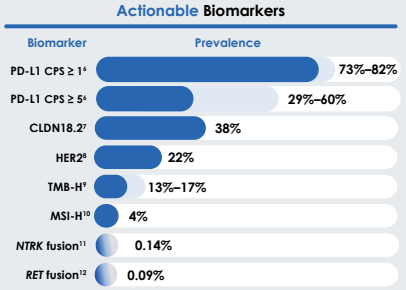
FGFR2b is a **receptor tyrosine kinase** primarily expressed on epithelial cells and involved in numerous cellular functions.[3]

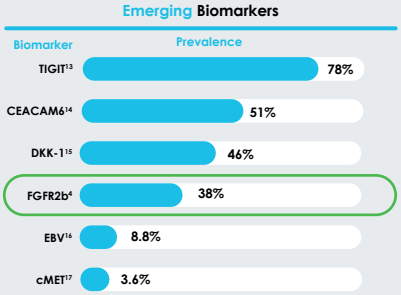
FGFR2b is an emerging protein biomarker overexpressed in ~ 38%‡ of patients with advanced gastric/GEJ cancer[4]

‡FGFR2b protein overexpression is defined as any percentage of tumor cells with moderate (2+) to strong (3+) membranous staining, as detected by IHC.

In addition to gastric cancer, FGFR2b is overexpressed in other cancers including esophageal, lung, breast, pancreatic, colorectal, and gynecological cancers.[3,5]

PREVALENCE OF BIOMARKERS IN PATIENTS WITH ADVANCED GASTRIC/GEJ CANCER



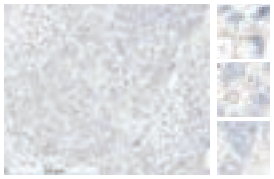


Advancements in tumor profiling have led to the identification of biomarkers that may have potential clinical utility for patients with advanced gastric/GEJ cancer[18]

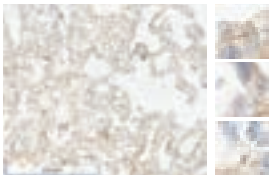
FGFR2b protein overexpression may be prognostic and associated with shorter survival in gastric/GEJ cancers[19,20]

FGFR2b PROTEIN OVEREXPRESSION CAN BE DETECTED BY IHC IN GASTRIC/GEJ CANCER[4,9,§]

FGFR2b protein overexpression is defined as the presence of moderate (2+) to strong (3+) membranous staining of tumor cells.[21,22]



FGFR2b in gastric adenocarcinoma with **no (0) staining**



FGFR2b in gastric adenocarcinoma with predominantly **weak (1+) staining**

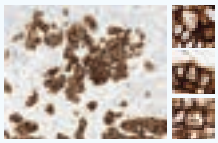
FGFR2b protein overexpression not detected in cell membrane[23]

No tumor cells with moderate to strong membranous staining **OR** tumor cells only exhibiting:

- Negative to weak membranous staining and/or
- Cytoplasmic-only staining at any intensity

FGFR2b Overexpression

FGFR2b in gastric adenocarcinoma with predominantly **moderate (2+) staining**



FGFR2b in gastric adenocarcinoma with predominantly **strong (3+) staining**

FGFR2b protein overexpression detected in cell membrane[23]

Any tumor cells with moderate to strong membranous staining, including any of the following:

- Basal-lateral
- Partial or complete circumferential
- Basal only
- Apical only

FGFR2b PROTEIN OVEREXPRESSION AND *FGFR2* GENE AMPLIFICATION ARE DISTINCT[21]

The phase 2, randomized, double-blind, placebo-controlled study of patients with advanced gastric/GEJ cancer showed that FGFR2b protein overexpression (detected by IHC) can occur in the absence of *FGFR2* gene amplification (detected by NGS); thus, IHC is the appropriate method to detect FGFR2b protein overexpression

BIOMARKER TESTING CONSIDERATIONS IN PATIENTS WITH GASTRIC CANCER

Biopsy

Multiple tissue biopsies (6–8) should be performed to provide adequate material for histologic and molecular interpretation.[24,25]

Ordering

Existing workflows for IHC biomarker testing may readily facilitate clinical integration of additional biomarker IHC assays.[26] Support the inclusion of all actionable IHC biomarkers to simplify the ordering process.[25-27]

Testing

Reflex testing protocols can accelerate biomarker result turnaround times, enhancing clinical decision-making efficiency.[28,29]

Results

Retaining biomarker test results in a patient's EHR may allow for easier access to providers as the landscape advances.[30]

Patient Management

Multidisciplinary tumor boards and other formal venues can help educate on effective biomarker testing strategies, evolving guidelines as well as targeted therapy approvals.[31-33]

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) recommend testing for certain actionable biomarkers, including HER2, PD-L1, MMR, and CLDN18.2, with IHC at diagnosis of metastatic gastric/GEJ cancers[24,34,]**

[§]Currently, FGFR2b testing is in the context of investigational clinical trials with no approved test in the market.[9] Roche Diagnostics has created the VENTANA® FGFR2b (FPR2-D) Mouse Monoclonal Antibody assay (Class 1) that recognizes the FGFR2b isoform via IHC.[35,36] **HER2 and CLDN18.2 testing in GEJ only for adenocarcinoma. IHC/ISH/targeted PCR is the preferred approach to assess biomarkers, initially. However, NGS testing through a CLIA-approved laboratory may be considered later in the clinical course of patients with sufficient tumor tissue available for testing.[24,34]

ABBREVIATIONS: AKT, protein kinase B; CEACAM6, carcinoembryonic antigen-related cell adhesion molecule 6; CLDN18.2, claudin-18 isoform 2; cMET, cellular mesenchymal-epithelial transition factor; CPS, combined positive score; DKK-1, Dickkopf-1; EBV, Epstein-Barr virus; EHR, electronic health record; FGF, fibroblast growth factor; FGFR, FGF receptor; FGFR2, FGF receptor 2; FGFR2b, FGFR2 isoform IIIb; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ITIM, immunoreceptor tyrosine-based inhibitory motif; MMR, mismatch repair; MAPK, mitogen-activated protein kinase; MSI-H, microsatellite instability-high; mTOR, mammalian target of rapamycin; NCCN, National Comprehensive Cancer Network; NGS, next-generation sequencing; NTRK, neurotrophic tyrosine receptor kinase; PCR, polymerase chain reaction; PD-L1, programmed cell death ligand 1; PI3K, phosphoinositide 3-kinase; RAS, rat sarcoma; RET, rearranged during transfection; TIGIT, T-cell immunoglobulin and ITIM domain; TMB-H, tumor mutational burden-high; US, United States.

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