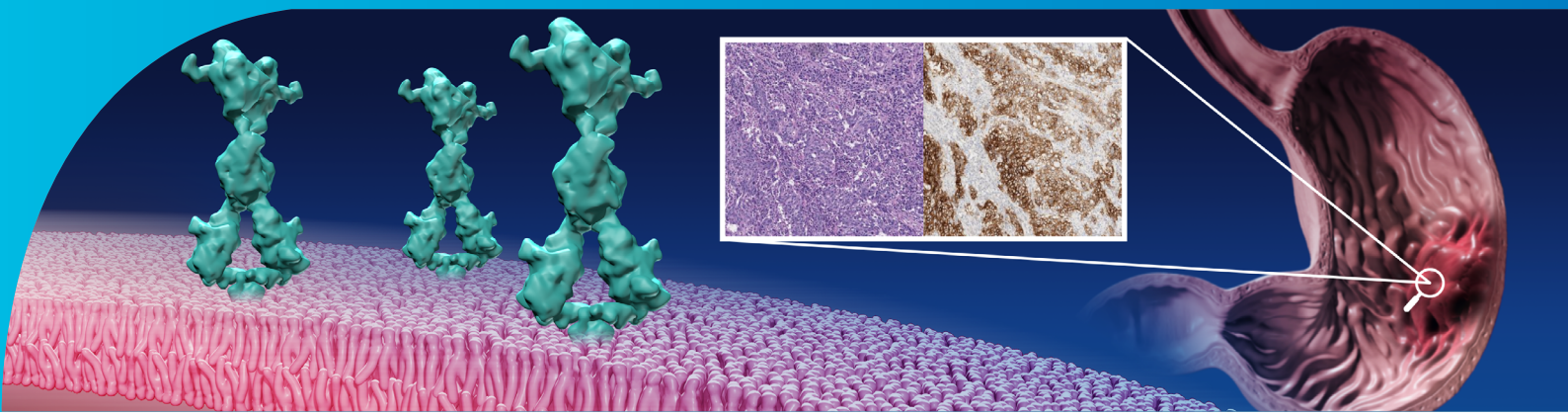
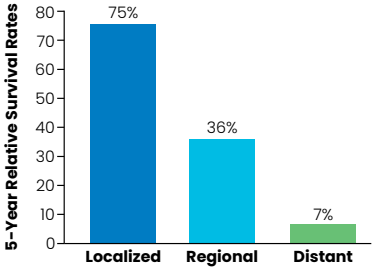
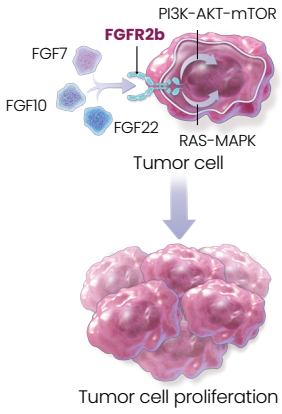
# **FGFR2b**—An Emerging Biomarker and Investigational Target in Gastric Cancer



5-Year Relative US Survival Rates by Stage of Diagnosis From 2014-2020[1]




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

**> 61%** of patients with gastric cancer present with advanced-stage disease[†] at the time of diagnosis in the US.[3]

The 5-year relative survival rate for patients with gastric cancer that includes distant metastasis at diagnosis is only 7% 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 26,890 estimated new cases in 2024.[4]

## OVEREXPRESSION OF FGFR2b PROTEIN DRIVES TUMORIGENESIS

**FGFR2b** is a **receptor tyrosine kinase** primarily expressed on epithelial cells and involved in numerous cellular functions.[5]

**FGFR2b protein overexpression is prevalent in 20%–30% of patients with advanced G/GEJ cancer.[6,7,‡]**

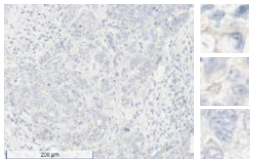
In addition to gastric cancer, FGFR2b is overexpressed in other cancers including esophageal, lung, breast, pancreatic, colorectal, and gynecological cancers.[5,8]

[‡]Approximate range from a phase 2 trial in patients with locally advanced or metastatic G/GEJ cancer. Of 910 prescreened patients, 274 (30%) were positive for FGFR2b with any 2+/3+ tumor cell staining by IHC; 155 of the any 2+/3+ positives underwent further testing with 98 (63%) exhibiting FGFR2b ≥ 10% 2+/3+ tumor cell staining by IHC; 63% extrapolated to the 274 any 2+/3+ positives estimates to ~ 20%.[6,7]

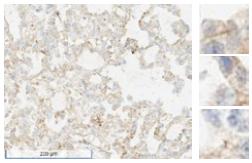
## PREVALENCE OF BIOMARKERS IN PATIENTS WITH ADVANCED G/GEJ CANCER


**Advancements in tumor profiling have led to the identification of biomarkers that may have potential clinical utility for patients with advanced G/GEJ cancer[21]**

**FGFR2b protein overexpression may be prognostic and associated with shorter survival in G/GEJ cancers[22,23]**



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



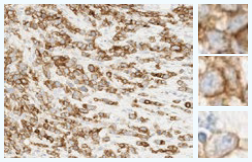
FGFR2b in gastric adenocarcinoma with predominantly **weak (1+) staining**

**FGFR2b protein overexpression not detected in cell membrane[24]**

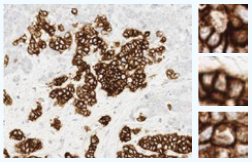
No tumor cells with moderate to strong membranous staining **OR** tumor cells only exhibiting:

- 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[24]**

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 CAN BE DETECTED BY IHC IN G/GEJ CANCER[24,*]

Protein overexpression is defined as the presence of moderate (2+) to strong (3+) membranous staining of tumor cells.[6,25]

FGFR2b protein overexpression may be associated with poor prognosis.[22,26]

*Currently, FGFR2b testing is in the context of investigational clinical trials with no approved test in the market.[12]

## FGFR2b PROTEIN OVEREXPRESSION AND *FGFR2* GENE AMPLIFICATION ARE DISTINCT AND MAY DEFINE DIFFERENT POPULATIONS

The phase 2 randomized, double-blind, placebo-controlled study of patients with metastatic G/GEJ cancer, demonstrates that more patients with FGFR2b protein overexpression can be identified with IHC than with ctDNA; thus, FGFR2b protein overexpression evaluation by IHC is not interchangeable with *FGFR2* gene amplification assessment.[6]

## 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.[27, 28]

### Ordering

Existing workflows for IHC biomarker testing may readily facilitate clinical integration of additional biomarker IHC assays.[29]
The average turnaround time for IHC is ~ 2-4 days.[30]

### Testing

Implementation of reflex testing protocols for gastric cancer biomarkers can lead to faster informed clinical decisions for patients.[31]

### Results

Retaining biomarker test results in a patient's EHR may allow for easier access to providers as the landscape advances.[32]

### 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.[30,33,34]

**NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Gastric Cancer recommend testing for certain actionable biomarkers upon diagnosis of metastatic gastric cancer, considering IHC/FISH/ targeted PCR first, followed by additional NGS[27]**

**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; ctDNA, circulating tumor DNA; 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; G/GEJ, gastric/gastroesophageal junction; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ITIM, immunoreceptor tyrosine-based inhibitory motif; MAPK, mitogen-activated protein kinase; MMR, mismatch repair; MSI-H, microsatellite instability-high; mTOR, mammalian target of rapamycin; NTRK, neurotrophic tyrosine receptor kinase; 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, tumor mutational burden; TMB-H, TMB-high; US, United States.

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