FGFR2b: An Emerging Target in G/GEJ Cancer

FGFR2b, fibroblast growth factor receptor 2, isoform IIIb; G/GEJ, gastric or gastroesophageal junction.

USA-OCF-82512

Objectives

1. Highlight the unmet needs and complex heterogeneity in G/GEJ cancer
2. Describe the biomarker landscape in G/GEJ cancer and the concept of precision medicine
3. Understand the role of FGFR2b in tumorigenesis and distinguish protein overexpression from gene amplification
4. Review biomarker testing considerations for G/GEJ cancer

FGFR2b, fibroblast growth factor receptor 2, isoform IIIb; G/GEJ, gastric or gastroesophageal junction.

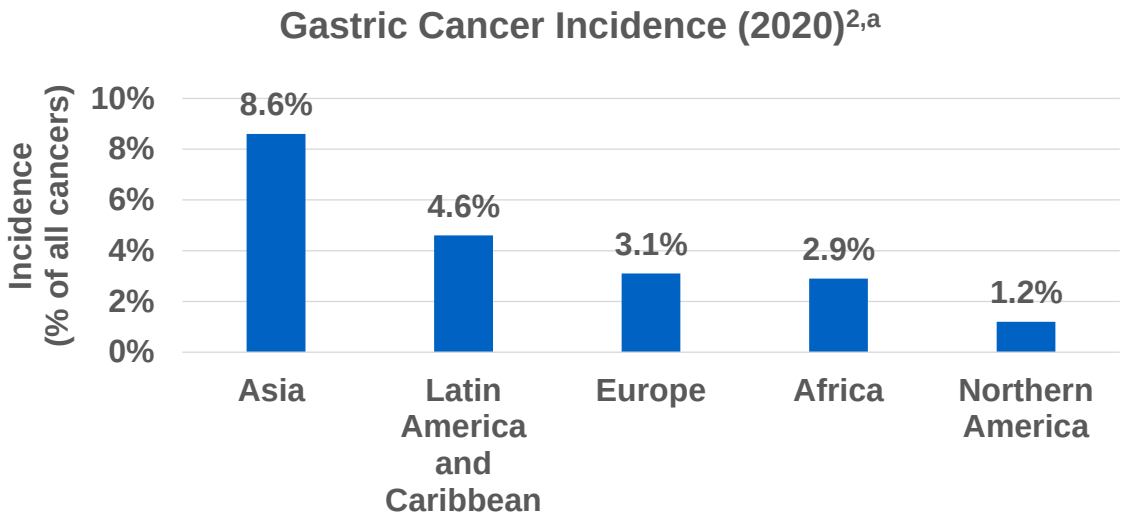
G/GEJ Cancer: Unmet Need and Complex Heterogeneity

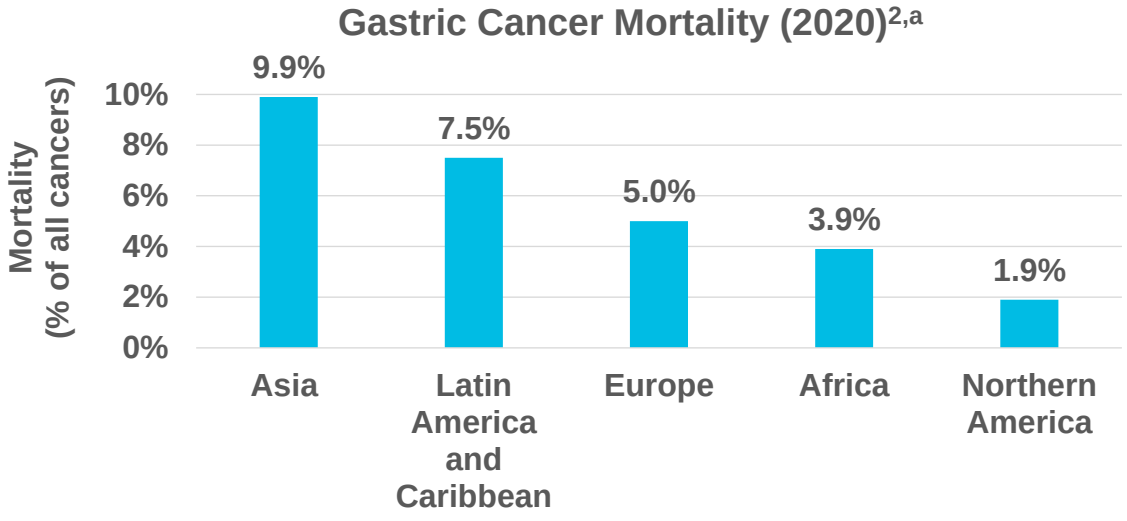
G/GEJ, gastric or gastroesophageal junction.

Gastric Cancer Is the Fifth Leading Cause of Cancer-Related Death Worldwide[1,*]

~1 million **new cases** of gastric cancer are diagnosed globally each year[1,*]

659,853 **deaths** are caused by gastric cancer globally each year[1,*]



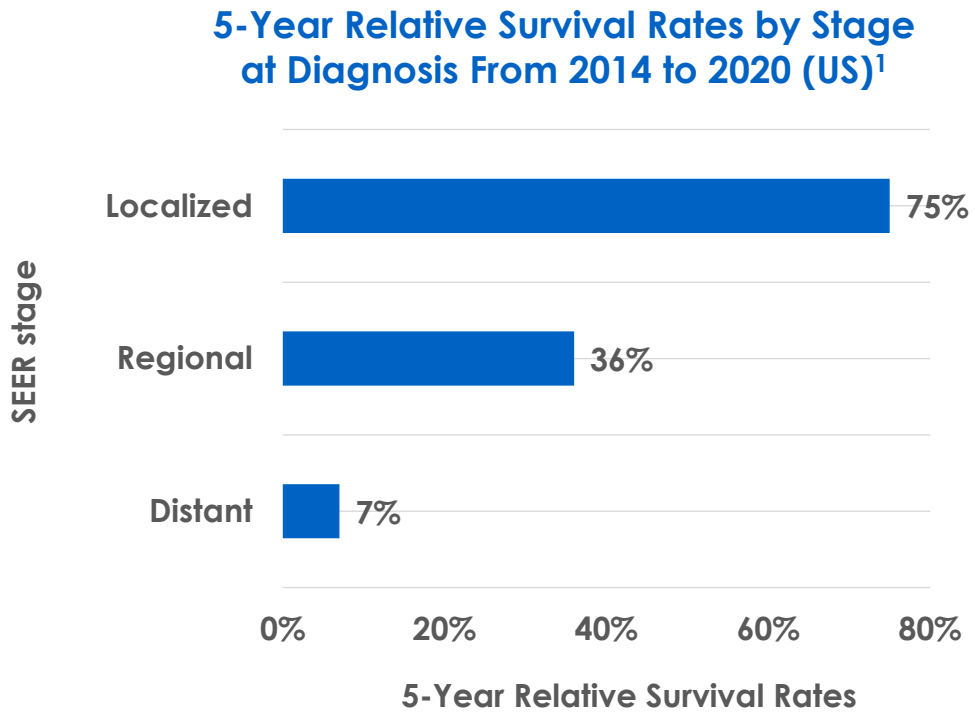


LOWERING THE GLOBAL INCIDENCE OF AND MORTALITY DUE TO GASTRIC CANCER REMAINS A SIGNIFICANT UNMET NEED

*Most gastric cancers (~ 95%) are adenocarcinomas, originating in the columnar epithelial cells in the stomach.[3]
[a]Based on GLOBOCAN 2020 data.[1]
GLOBOCAN, Global Cancer Observatory.

1. Bray F, et al. *CA Cancer J Clin. 2024.* doi:10.3322/caac.21834. **2.** World Health Organization. www.gco.iarc.com. Accessed August 24, 2023.

Most Patients With Gastric Cancer Are Diagnosed at an Advanced Stage With Low Rates of Survival[1]



61% of patients with gastric cancer have **advanced disease*** at the time of diagnosis[1]

EARLY DETECTION OF CANCER MAY IMPROVE PATIENT OUTCOMES; HOWEVER, SIGNS AND SYMPTOMS OF EARLY DISEASE MAY BE DIFFICULT TO SPOT, LEADING TO DELAYS IN DIAGNOSIS AND POOR SURVIVAL[1,2]

*This includes patients with regional disease, or those whose cancer have spread to regional lymph nodes, and metastatic disease at the time of diagnosis. There are 26,890 estimated new cases.[1]
SEER, Surveillance, Epidemiology, and End Results program; US, United States.

1. National Cancer Institute. https://seer.cancer.gov/statfacts/html/stomach.html. Accessed April 17, 2024. **2.** GBD 2017 Stomach Cancer Collaborators. *Lancet Gastroenterol Hepatol.* 2020;5:42-54.

Survival Rates of Gastric Cancer Have Improved Owing to Earlier Diagnosis and Treatment

5-Year Net Survival Rates for Patients With Gastric Cancer (2010–2014)

United States

33.1%[a]

United Kingdom

20.7%[a]

Japan

60.3%[b]

South Korea

68.9%[b]

ACCORDING TO A REPORT FROM THE GLOBAL SURVEILLANCE OF TRENDS IN CANCER SURVIVAL PROGRAMS, THE AGE-STANDARDIZED 5-YEAR NET SURVIVAL RATE FOR GASTRIC CANCER STILL RANGES BETWEEN 20% AND 40% IN MANY COUNTRIES

[a]Gastric cancers tend to be detected at an advanced stage. [b]Early detection of gastric cancer is considered to have contributed to favorable survival in these countries.
Sekiguchi M, et al. *Digestion*. 2022;103:22-28.

AMGEN

Gastric Cancer Can Be Attributed to Multiple Environmental and Genetic Risk Factors

Helicobacter pylori	*H. pylori* infections are the main cause of gastric cancer, accounting for ~ 89% of cases[1]
Age	In addition to the rising incidence and risk of age-related disease due to the increase in global life expectancy,[2] incidence rates are also increasing among younger populations in countries with historically low incidence[3]
Sex	Gastric cancer is two times more likely to develop in males than females[4]
Obesity	The rapid increase in the global prevalence of obesity, which may induce stomach lining inflammation, is linked to an increase in gastric cancer burden[5,6]
Diet and Alcohol	High salt content, preserved foods, and > 3 alcoholic drinks per day can increase the risk of gastric cancer[7]
Genetics	Inherited genetic mutations,* family history of gastric cancer, and type A blood are associated with a higher risk of gastric cancer[5,7]

WHILE AGING AND OTHER RISK FACTORS (EG, OBESITY, DIET, SEX, GENETICS) CONTRIBUTE TO GASTRIC CANCER, INCIDENCE IS ALSO INCREASING AMONG YOUNGER POPULATIONS[8]

*Including mutations in *CDH1, CTNNA1, MLH1, MSH2, APC, MSH6, PMS2, TP53, STK11, SMAD4, BMPR1A,* and *EPCAM*.[9]

APC, adenomatous polyposis coli; BMPR1A, bone morphogenetic protein receptor type 1A; CDH1, cadherin-1; CTNNA1, catenin alpha 1; EPCAM, epithelial cellular adhesion molecule; MLH1, mutL homolog 1; MSH2, mutS homolog 2; MSH6, mutS homolog 6; PMS2, PMS1 protein homolog 2, mismatch repair system component; SMAD4, SMAD family member 4; STK11, serine/threonine kinase 11; TP53, tumor protein 53.

1. Balakrishnan M, et al. *Curr Gastroenterol Rep*. 2017;19:36. **2.** Yan C, et al. *Chin Med J (Engl)*. 2023;136:397-406. **3.** Arnold M, et al. *Gut*. 2020;69:823-829. **4.** Sung H, et al. *CA Cancer J Clin*. 2021;71:209-249. **5.** Rawla P, et al. *Prz Gastroenterol*. 2019;14:26-38. **6.** Karczewski J, et al. *Dig Dis Sci*. 2019;64:2740-2749. **7.** American Cancer Society. https://www.cancer.org/content/dam/CRC/PDF/Public/8839.00.pdf. Accessed August 20, 2023. **8.** Schell D, et al. *Cancers*. 2022;14:275. **9.** Seppälä TT, et al. *BJS Open*. 2023;7:zrad023.

G/GEJ Cancer Is a Complex and Heterogenous Disease

Classification Parameters

Tumor Location (per AJCC 8th edition)[1]

Tumor involves EGJ and epicenter ≤ 2 cm into the proximal stomach (esophageal cancer)

Tumor involves EGJ and epicenter > 2 cm into the proximal stomach (stomach cancer)

Tumor does not involve EGJ and is cardia cancer (stomach cancer)

Histology[2]

Intestinal/well-differentiated (85%–90%)

Diffuse/undifferentiated (10%–15%)

Mixed subtype

Etiology[2]

Sporadic (90%–95%)

Familial predisposition (5%–10%)

WHILE HISTORICAL CLASSIFICATION SYSTEMS INFORM PROGNOSIS AND TREATMENT DECISIONS, PROGRESS IN TREATING G/GEJ CANCER HAS BEEN ELUSIVE DUE TO CONSIDERABLE TUMOR HETEROGENEITY IN G/GEJ CANCER[3,4]

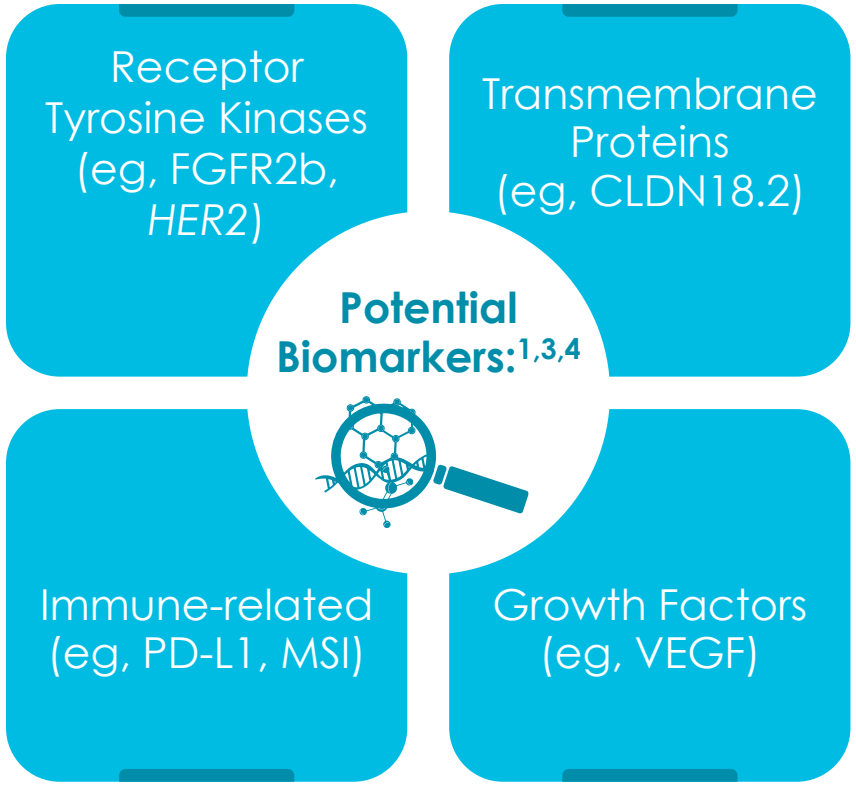
AJCC, American Joint Committee on Cancer; EGJ, esophagogastric junction; G/GEJ, gastric or gastroesophageal junction.

1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Gastric Cancer V.2.2023. © National Comprehensive Cancer Network, Inc. 2023. All rights reserved. Accessed August 24, 2023. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. **2.** De Mello RA, et al. *Am Soc Clin Oncol Educ Book*. 2018;38:249-261. **3.** Ajani JA. *Transl Gastroenterol Hepatol*. 2021;6:49. **4.** The Cancer Genome Atlas Network. *Nature*. 2014;513:202-209.

G/GEJ Cancer Is a Complex and Heterogenous Disease (Continued)

Classification Systems

TCGA Classification[1]	ACRG Classification[2]
EBV-positive	MSI-high
MSI	MSS with wild-type p53
Genomically stable tumors	MSS with mutant p53
Chromosomal instability	MSS and epithelial-mesenchymal transition–like



MOLECULAR CHARACTERIZATION OF G/GEJ CANCER CAN INFORM PATIENT MANAGEMENT

ACRG, Asian Cancer Research Group; CLDN18.2, claudin-18 isoform 2; EBV, Epstein-Barr virus; FGFR2b, fibroblast growth factor receptor 2, isoform IIIb; G/GEJ, gastric or gastroesophageal junction; HER2, human epidermal growth factor receptor 2; MSI, microsatellite instability; MSS, microsatellite stable; PD-L1, programmed death-ligand 1; TCGA, The Cancer Genomic Atlas; VEGF, vascular endothelial growth factor.

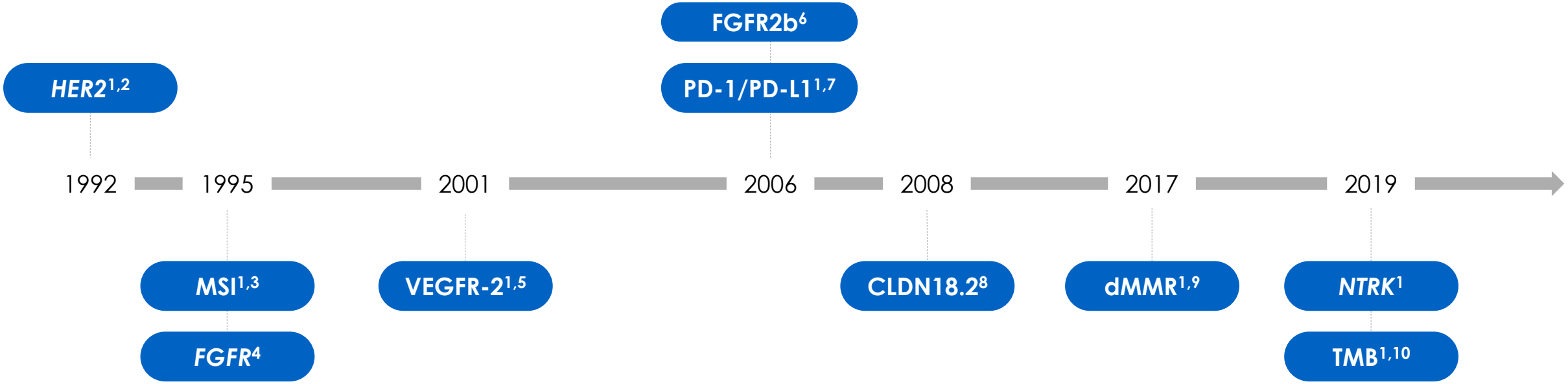
1. The Cancer Genome Atlas Network. *Nature*. 2014;513:202-209. **2.** Daun T, et al. *Cancers (Basel)*. 2021;13:3722. **3.** Fontana E, et al. *Ther Adv Med Oncol*. 2016;8:113-125.
4. Yang B, et al. *J Exp Clin Cancer Res*. 2019;38:283.

Biomarkers in G/GEJ Cancer and a Path for Precision Medicine

G/GEJ, gastric or gastroesophageal junction.

Identification of Potential G/GEJ Cancer Biomarkers Has Prompted the Investigation of Targeted Therapies

First Appearance of G/GEJ Biomarkers in Peer-Reviewed Literature



FGFR2b IS AMONG SEVERAL BIOMARKERS IN THE G/GEJ CANCER LANDSCAPE THAT ARE UNDER CLINICAL INVESTIGATION[11]

CLDN18.2, claudin-18 isoform 2; dMMR, mismatch repair deficient; FGFR, fibroblast growth factor receptor; FGFR2b, FGFR 2, isoform IIIb; G/GEJ, gastric or gastroesophageal junction; HER2, human epidermal growth factor receptor 2; MSI, microsatellite instability; NTRK, neurotrophic tyrosine receptor kinase; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; TMB, tumor mutational burden; VEGFR-2, vascular endothelial growth factor receptor-2.

1. ACS. https://www.cancer.org/content/dam/CRC/PDF/Public/8841.00.pdf. Accessed August 20, 2023. **2.** Jaehne J, et al. *J Cancer Res Clin Oncol*. 1992;118:474-479. **3.** Nakashima H, et al. *Int J Cancer*. 1995;64:239-242. **4.** Ueki T, et al. *J Pathol*. 1995;177:353-361. **5.** Tian X, et al. *Biochem Biophys Res Commun*. 2001;286:505-512. **6.** Matsunobu T, et al. *Int J Oncol*. 2006;28:307-314. **7.** Wu C, et al. *Acta Histochem*. 2006;108:19-24. **8.** Sahin U, et al. *Clin Cancer Res*. 2008;14:7624-7634. **9.** Le DT, et al. *Science*. 2017;357:409-413. **10.** Samstein RM, et al. *Nat Genet*. 2019;51:202-206. **11.** Ahn S, et al. *Mod Pathol*. 2016;29:1095-1103.

Biomarker Prevalence and Detection in G/GEJ Cancer[1-10]

Biomarker	Prevalence in G/GEJ Cancer	Detection Method	Preferred Sample
ERBB2/HER2[1,2]	22%	IHC and FISH	Tissue
MSI-high[3,4]	8.8%–15%	IHC and NGS; PCR	Tissue; DNA extracted from tissue
EBV-positive[5]	8.77%	ISH	Tissue
PD-L1[6]	82% CPS ≥ 1% 60% CPS ≥ 5%	IHC	Tissue
FGFR2b protein overexpression[7]	20%–30%[a]	IHC	Tissue
CLDN18.2[8]	38%[b]	IHC	Tissue
Tumor profiling[9-11]	NTRK, EGFR, MET amplification	NGS for NTRK[9]; IHC/FISH for EGFR[10]; ISH for MET[11]	Tissue
Circulating tumor DNA[12]	Monitor response after treatment and/or early detection of tumor recurrence	NGS and ddPCR	Blood plasma

[a]Approximate range based on 910 pre-screened patients for a phase 2 trial in locally advanced or metastatic G/GEJ cancer, of which 274 patients (30%) were prescreened positive for FGFR2b any 2+/3+ tumor cell staining by IHC, and on the 155 enrolled subjects, of which 96 subjects (62%) exhibited FGFR2b ≥ 10% 2+/3+ tumor cell staining by IHC.[7] [b]The cutoff for CLDN18.2 positivity was adapted (from ≥ 70% in FAST to ≥ 75% in SPOTLIGHT).[8]

CLDN18.2, claudin-18 isoform 2; CPS, combined positive score; ddPCR, digital droplet polymerase chain reaction; DNA, deoxyribonucleic acid; EBV, Epstein-Barr virus; EGFR, epidermal growth factor receptor; ERBB2, erythroblastic oncogene B; FGFR2b, fibroblast growth factor receptor 2, isoform IIIb; FISH, fluorescence in situ hybridization; G/GEJ, gastric or gastroesophageal junction; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; MET, mesenchymal epithelial transition factor receptor; MSI, microsatellite instability; NGS, next-generation sequencing; NTRK, neurotrophic tyrosine receptor kinase; PCR, polymerase chain reaction; PD-L1, programmed death-ligand 1.

1. Van Cutsem E, et al. *Gastric Cancer*. 2015;18:476-484. **2.** Kelly CM, et al. *J Gastrointest Oncol*. 2016;7:750-762. **3.** Vos EL, et al. *J Clin Oncol*. 2021;39:244. **4.** Quaas A, et al. *Eur J Cancer*. 2022;173:95-104. **5.** Tavakoli A, et al. *BMC Cancer*. 2020;20:493. **6.** Schoemig-Markiefka B, et al. *Gastric Cancer*. 2021;24:1115-1122. **7.** Wainberg ZA, et al. *Lancet Oncol*. 2022;23:1430-1440. **8.** Shitara K, et al. *Lancet*. 2023;401:1655-1668. **9.** Kim M, et al. *J Gastric Cancer*. 2022;22:273-305. **10.** Arienti C, et al. *Front Oncol.* 2019;9:1308. **11.** Van Herpe, et al. *Cancers (Basel)*. 2023;15:1976. **12.** Suzuki T, et al. *Oncotarget*. 2020;11:3198-3207.

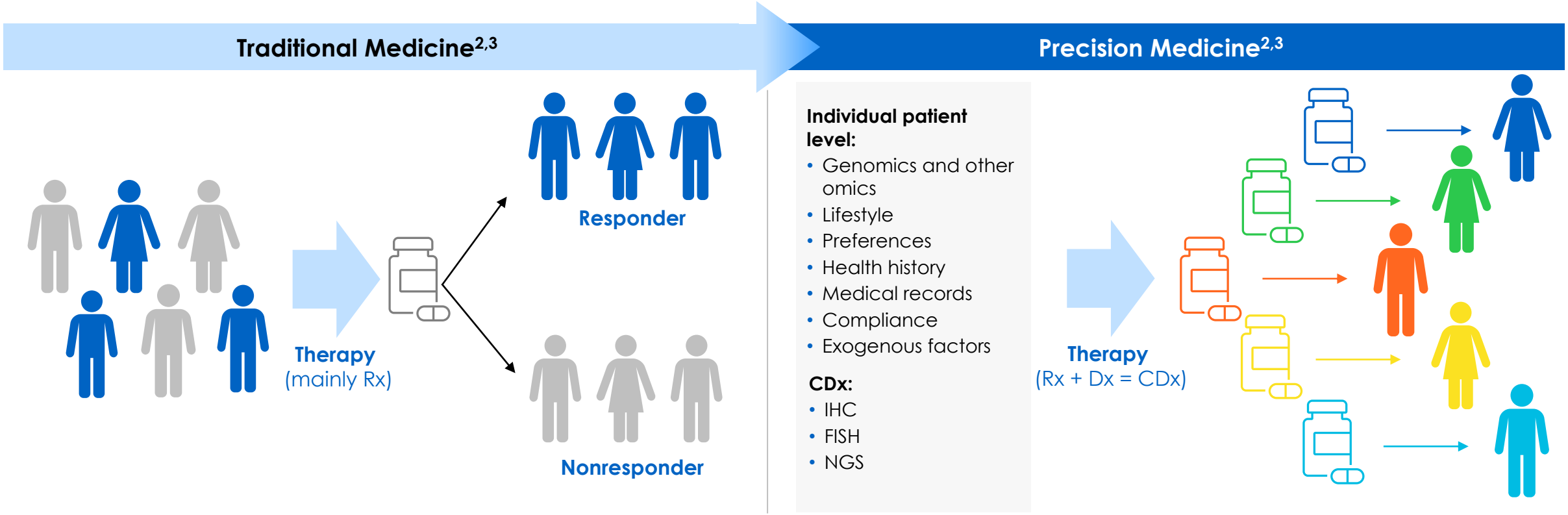
Biomarker Overlap in G/GEJ Cancer[1-5]

% (n/N)	CLDN18.2+ 24%[1,a] (98/408)	MSI-High 4.3%[3] (16/373)	HER2 9.9%[4] (11/111)	PD-L1+	
				43.2%[4,c] (48/111)	62%[5,c] (241/389)
HER2+	15 (15/98)	-	-	-	14.5 (35/241)
dMMR/MSI	5 (5/98)	-	-	-	8.3 (20/241)
PD-L1– CPS < 1	26 (24/98)	-	54.5 (6/11)	-	-
PD-L1+ CPS ≥ 5	42 (39/98)	50[3,b] (8/16)	45.5[c] (5/11)	-	-
Diffuse type	48 (47/98)	-	-	50 (24/48)	47.3 (114/241)
Intestinal type	52 (51/98)	-	-	50 (24/48)	36.5 (88/241)
Mixed/other	-	-	-	-	13.2 (32/241)

[a]CLDN18.2+ as ≥ 75% tumor cells with 2+/3+ membrane staining.[1] [b]Staining on ≥ 1% of tumor cells was considered positive.[3] [c]CPS ≥ 1.[4]
CLDN18.2, claudin-18 isoform 2; CPS, combined positive score; dMMR, deficient mismatch repair; G/GEJ, gastric or gastroesophageal junction; HER2, human epidermal growth factor receptor 2; MSI, microsatellite instability; PD-L1, programmed death-ligand 1.

1. Klempner SJ, et al. *ESMO Open*. 2023;8:100778. **2.** Shitara K, et al. Poster presented at: ASCO Annual Meeting; June 2-6, 2023; Chicago, IL. Poster 4035.
3. Vanderwalde A, et al. *Cancer Med.* 2018;7:746-756. **4.** Attia S, et al. *Asian Pac J Cancer Prev*. 2022;23:1433-1444. **5.** Yoshida T, et al. *Cancer Biol Ther*. 2022;23:191-200.

Targeted Therapies May Improve Outcomes for Patients With Metastatic G/GEJ Cancer[1]



TESTING PATIENTS WITH METASTATIC G/GEJ CANCER FOR BIOMARKERS CAN PROVIDE INSIGHT INTO A PATIENT'S TREATMENT PLAN[4,5]

CDx, companion diagnostic; Dx, diagnosis; FISH, fluorescence in situ hybridization; G/GEJ, gastric or gastroesophageal junction; IHC, immunohistochemistry; NGS, next-generation sequencing; Rx, medical prescription.

1. Salati M, et al. *ESMO Open.* 2017;2:e000206. **2.** Malone ER, et al. *Genome Med.* 2020;12:8. **3.** Forbes. www.forbes.com. Accessed August 24, 2023. **4.** American Cancer Society. https://www.fightcancer.org/sites/default/files/Improving%20Access%20to%20Biomarker%20Testing_FINAL.pdf. Accessed August 20, 2023. **5.** Catenacci DVT, et al. *Future Oncol.* 2019;15:2073-2082.

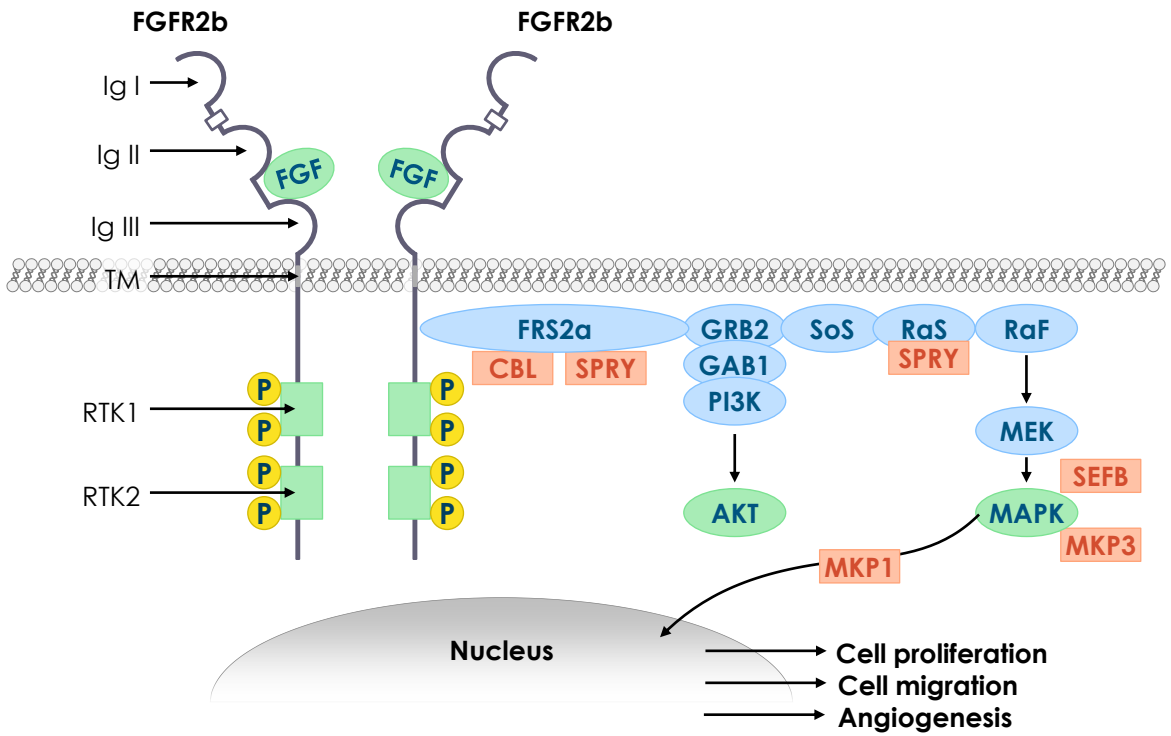
FGFR2b Expression in Tumorigenesis

FGFR2b, fibroblast growth factor receptor 2, isoform IIIb.

The FGFR2b Protein Is an RTK Involved in Numerous Cellular Functions[1-4]

- FGFR2b is one of the protein isoforms of the *FGFR2* gene (FGFR2 isoform IIIb)[2]
- It is primarily expressed in epithelial cells[2]
  - Due to its unique extracellular domain, only a specific subset of FGF ligands will bind to the receptor
- Ligand binding and homodimerization activate downstream signaling pathways, including the PI3K-AKT and RAS-MAPK pathways, that function in cell proliferation, migration, and angiogenesis[1,3]

FGFR2b Drives Multiple Cellular Functions[1,4]

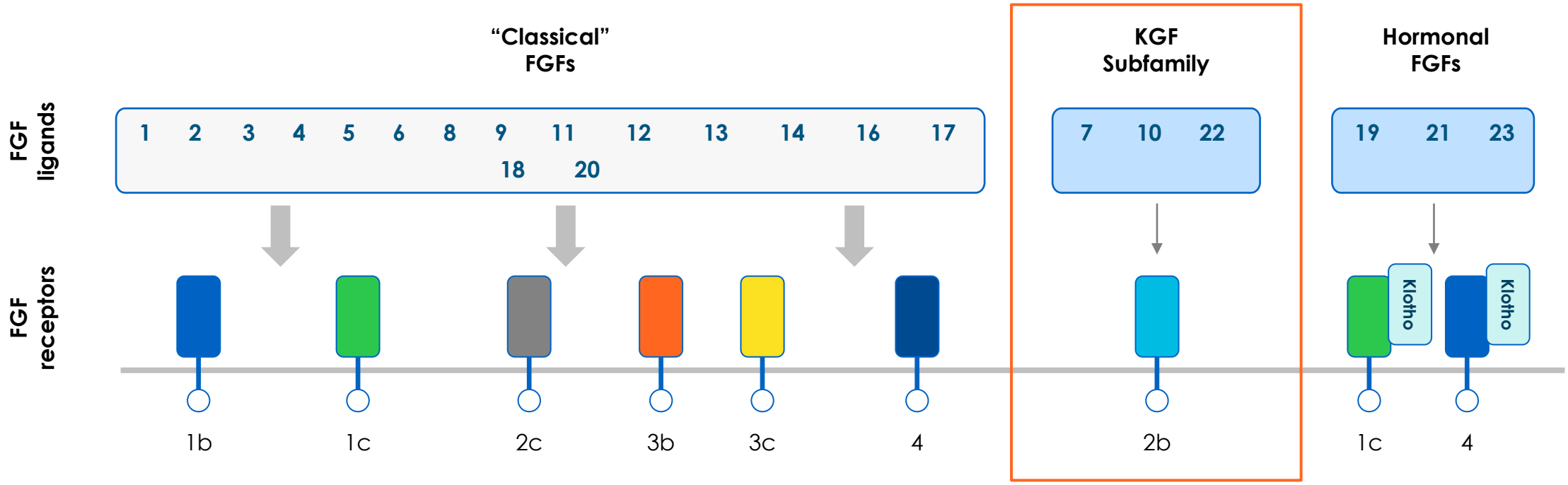


AKT, protein kinase B; CBL, Casitas B lineage lymphoma; FGF, fibroblast growth factor; FGFR2, FGF receptor 2; FGFR2b, FGFR2, isoform IIIb; FRS2a, FGFR substrate 2a; GAB1, GRB2-associated-binding protein 1; GRB2, growth factor receptor-bound 2; Ig, immunoglobulin; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase kinase; MKP1, mitogen-activated protein kinase phosphatase 1; MKP3, mitogen-activated protein kinase phosphatase 3; P, phosphate; PI3K, phosphoinositide 3-kinase; RaF, proto-oncogene, serine/threonine kinase; RAS, rat sarcoma; RTK, receptor tyrosine kinase; SAM, S-adenosyl methionine; SEFB, SAM-dependent methyltransferase; SoS, son of sevenless; SPRY, sprouty protein; TM, transmembrane.

1. Turner N, et al. *Nat Rev Cancer*. 2010;10:116-120. **2.** Ishiwata T. *Front Biosci (Landmark Ed)*. 2018;23:626-639. **3.** Del Piccolo N, et al. *J Biol Chem*. 2017;292:1288-1301. **4.** Khosravi F, et al. *Front Cell Dev Biol*. 2021;9:672935.

A Unique Subset of FGF Ligands Bind With High Specificity to FGFR2b

Specificity of the FGF Family of Ligands for Different FGF Receptors

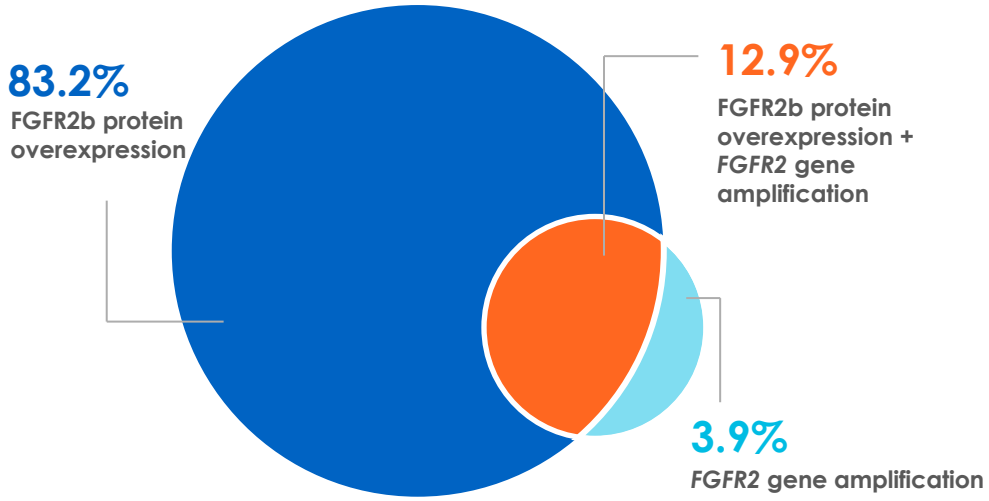


FGF, fibroblast growth factor; FGFR, FGF receptor; KGF; keratinocyte growth factor.
Powers J, et al. Presented at: American Association for Cancer Research 10th Annual Meeting; April 16-20, 2016; New Orleans, LA. Abstract 1636.

FGFR2b Protein Overexpression and *FGFR2* Gene Amplification Are Distinct[1-4]

- **Gene amplification** is an increase in the copy of a specific gene, which may lead to protein overexpression[2]
- **Protein overexpression** is the overabundance of a specific protein[3]
- In addition to gene amplification, other biological processes (eg, dysregulated protein synthesis and degradation) can result in protein overexpression[4]

FGFR2 Gene Amplification/FGFR2b Protein Overexpression Status of Patients With G/GEJ Cancer[1,*]



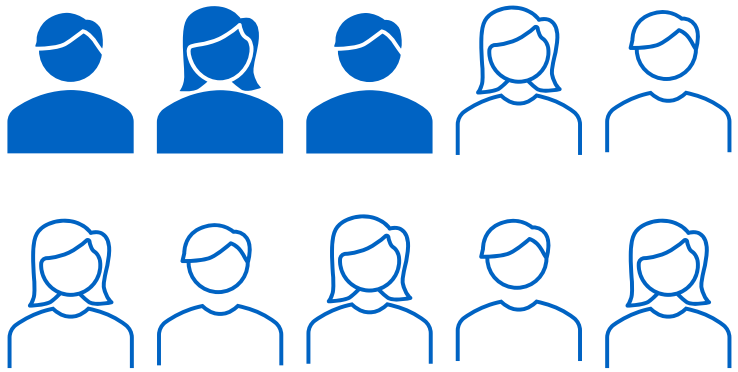
FGFR2b protein overexpression = evaluated by IHC;
FGFR2 gene amplification = evaluated by ctDNA analysis

FGFR2b PROTEIN OVEREXPRESSION (MEASURED BY IHC) CAN BE INDEPENDENT OF *FGFR2* GENE AMPLIFICATION (MEASURED USING NGS/PCR)[1,5]

*Data from a 2021 randomized, double-blind, placebo-controlled, phase 2 study of patients (N = 155) with metastatic G/GEJ cancer.[1]
ctDNA, circulating tumor deoxyribonucleic acid; FGFR2, fibroblast growth factor receptor 2; FGFR2b, FGFR2, isoform IIIb; G/GEJ, gastric or gastroesophageal junction; IHC, immunohistochemistry; NGS, next-generation sequencing; PCR, polymerase chain reaction.

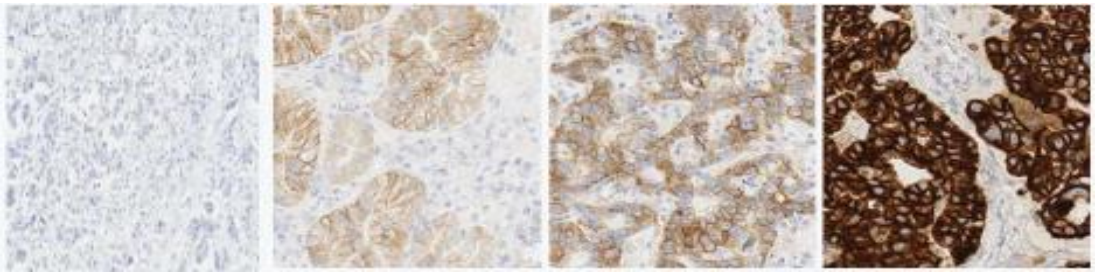
1. Wainberg ZA, et al. Presented at: American Society of Clinical Oncology Gastrointestinal Cancer Symposium; January 15-17, 2021; Online Virtual Scientific Program. Abstract LBA160. **2.** National Cancer Institute. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/gene-amplification. Accessed August 21, 2023. **3.** Bolognesi B, et al. *Elife*. 2018;7:e39804. **4.** Du Z, et al. *Mol Cancer*. 2018;17:58. **5.** Sato Y, et al. Novel biomarkers of gastric cancer: Current research and future perspectives. *J Clin Med*. 2023;12:4646.

FGFR2b Protein Is Overexpressed in Some Patients With G/GEJ Cancer and May Be Associated With Poor Prognosis[1-4]



~ 3 in 10 patients with metastatic G/GEJ cancer overexpress the FGFR2b protein[1,4,*]

FGFR2b Protein Overexpression by IHC Is Defined as 2+/3+ Staining[1]



No Staining (0)	Low–Moderate (1+)	Moderate–Strong (2+)	Strong (3+)

- FGFR2b overexpression was more frequent in tumors with poorly differentiated ($P < 0.001$) and diffuse-type histology ($P = 0.010$)[2,†]
- Patients with FGFR2b-overexpressed gastric cancer and an H-score[‡] ≥ 150 showed significantly shorter overall survival ($P = 0.001$)[2]

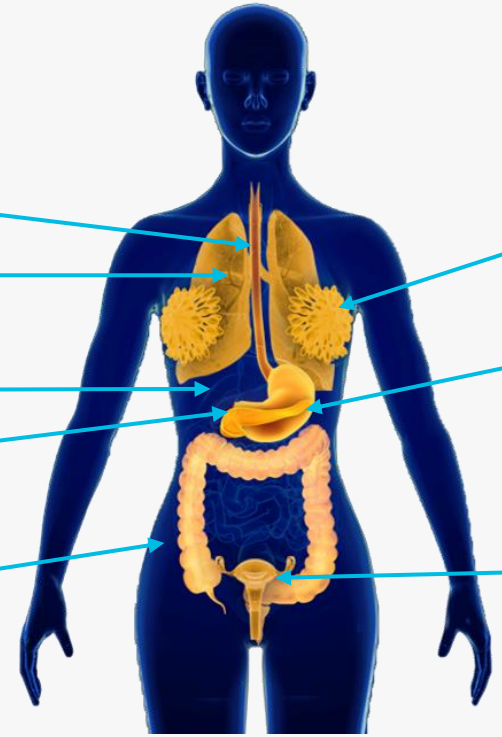
THE PREVALENCE OF FGFR2b OVEREXPRESSION IN G/GEJ CANCER (20%–30%)[§] AND ITS POTENTIAL ASSOCIATION WITH POOR PROGNOSIS MAKE FGFR2b A TARGET THAT WARRANTS FURTHER INVESTIGATION[1-4]

*Data from a randomized, double-blind, placebo-controlled, phase 2 study with a protocol allowing FGFR2b analyses on both fresh and archival samples (a majority of analyses were performed on fresh samples).[1,4] †Diffuse-type histology defined per Lauren classification.[2] ‡H-score is the sum of the percentage of stained tumor cells multiplied by an ordinal value corresponding to the intensity (0 = none, 1 = 1+, 2 = 2+, and 3 = 3+) and ranges from 0 to 300.[2] §Approximate range based on 910 pre-screened patients for a phase 2 trial in locally advanced or metastatic G/GEJ cancer, of which 274 patients (30%) were prescreened positive for FGFR2b any 2+/3+ tumor cell staining by IHC, and on the 155 enrolled subjects, of which 96 subjects (62%) exhibited FGFR2b ≥ 10% 2+/3+ tumor cell staining by IHC.[4]

FGFR2b, fibroblast growth factor receptor 2, isoform IIIb; G/GEJ, gastric or gastroesophageal junction; IHC, immunohistochemistry.

1. Catenacci D, et al. Presented at: American Society of Clinical Oncology Gastrointestinal Cancer Symposium; May 20, 2021; Online Virtual Scientific Program. Abstract 4010.
2. Ahn S, et al. *Mod Pathol*. 2016;29:1095-1103. **3.** Ishiwata T. *Front Biosci (Landmark Ed)*. 2018;23:626-639. **4.** Wainberg ZA, et al. *Lancet Oncol*. 2022;23:1430-1440.

The FGFR2b Protein Is Expressed in Various Tumors[1-4]



- Esophageal cancer[1]
- Lung cancer[1]
- iCCA[2]
- Pancreatic cancer[1]
- Colorectal cancer[1]
- Breast cancer[1]
- G/GEJ cancer[3]
- Gynecological cancers:
  - Uterine cervical[1]
  - Endometrial[1]
  - Ovarian cancer[1]

FGFR2b expression levels reported in the literature are limited and employ varying testing methodologies and scoring algorithms to define FGFR2b positivity.

CLINICALLY MEANINGFUL EXPRESSION RATES OF FGFR2b ACROSS TUMOR TYPES, DISEASE STAGES, AND LINES OF THERAPY MAY VARY AND ARE AN AREA OF ACTIVE INVESTIGATIONAL INTEREST[1-4]

FGFR2b, fibroblast growth factor receptor 2, isoform IIIb; G/GEJ, gastric or gastroesophageal junction; iCCA, intrahepatic cholangiocarcinoma.

1. Ishiwata T. *Front Biosci (Landmark Ed)*. 2018;23:626-639. **2.** Uson Jr PLS, et al. *Dig Dis Sci*. 2022;67:3797-3805. **3.** Wainberg ZA, et al. Presented at: American Society of Clinical Oncology Gastrointestinal Cancer Symposium; January 15-17, 2021; Online Virtual Scientific Program. Abstract LBA160. **4.** ClinicalTrials.gov. https://classic.clinicaltrials.gov/ct2/show/NCT05325866. Accessed August 19, 2023.

Biomarker Testing Considerations for Patients With G/GEJ Cancer

G/GEJ, gastric or gastroesophageal junction.

IHC for G/GEJ Cancer Biomarker Detection of Tissue Biopsies[1-8,*]

Routine[1,2]	Turnaround Time[2,3]	Sensitivity[4]	Specificity[3,5]
Testing modality used to assess key G/GEJ cancer biomarkers (eg, HER2, PD-L1)	Typically 1–4 days	IHC provides diagnostic guidance with sensitivity (up to 100%)†	Specificity with concordance across assay types (eg, 97%‡)

CONSIDERATION SHOULD BE GIVEN TO ENSURE ADEQUATE TISSUE IS AVAILABLE TO PERFORM ALL DIAGNOSTIC TESTING[6]

*Cytological specimens that contain circulating tumor cells can be used to test for and detect molecular biomarkers in patients with metastatic disease.[7] †Sensitivity of IHC assays depend on pretreatment conditions, antibody clones, and signal detection systems.[8] ‡Concordance between 22C3 and 28-8 pharmDx assays was 97% in 3,050 matched samples with PD-L1 expression data for both assays.[3]
G/GEJ, gastric or gastroesophageal junction; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; PD-L1, programmed death-ligand 1.

1. Ye DM, et al. *Oncol Lett*. 2020;19:17-29. **2.** Oncology PRO. https://oncologypro.esmo.org/oncology-in-practice/anti-cancer-agents-and-biological-therapy/targeting-ntrk-gene-fusions/importance-of-testing-cancers-for-ntrk-gene-fusions/general-challenges-of-testing-for-cancers-with-ntrk-gene-fusion/immunohistochemistry-ihc/advantages Accessed August 21, 2023.
3. Krigsfeld GS, et al. *J Clin Pathol*. 2020;73:656-664. **4.** Sukswai N, et al. *Curr Hematol Malig Rep*. 2019;14:368-375. **5.** Aggarwal C, et al. *Nat Rev Clin Oncol*. 2021;18:56-62.
6. Aisner DL, et al. *Arch Pathol Lab Med*. 2016;140:1206-1220. **7.** Matsuoka T, et al. *World J Gastroeneterol*. 2018;24:2818-2832. **8.** Nitta H, et al. *Pathol Int*. 2016;66:313-324.

Considerations for Biomarker Testing in Patients With G/GEJ Cancer[1-6]

Optimizing Tissue Acquisition

- Effective communication between tissue acquirers and pathologists may help sufficient tissue quantity and quality for biomarker testing[1]
- Multiple (~ 6–8) biopsies should be performed to provide adequate material for histological and molecular interpretation[2,3]
- Tissue acquisition procedures for biomarker testing should minimize risk to the patient while ensuring adequate tissue yield[1]

Preparing and Reporting Test Results

- Pathologists and oncologists can support the development of reflex testing protocols to:
  - Reduce turnaround time for acquisition of biomarker testing results[4]
  - Decrease time to treatment plan[4]
- Documenting test results in patient's electronic health record may allow for easier provider access and results retrieval throughout the patient journey[1]

Staying Current With Rapidly Evolving Practice Standards

- Consider multidisciplinary tumor boards and other formal venues to educate on:
  - Biomarker testing strategies[1,5,6]
  - Evolving guidelines[1]

G/GEJ, gastric or gastroesophageal junction.

1. Levy BP, et al. *Oncologist*. 2015;20:1175-1181. **2.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Gastric Cancer V.2.2023. © National Comprehensive Cancer Network, Inc. 2023. All rights reserved. Accessed August 24, 2023. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. **3.** Lordick F, et al. *Ann Oncol*. 2022;33:1005-1020. **4.** Gregg JP, et al. *Transl Lung Cancer Res*. 2019;8:286-301. **5.** van der Velden DL, et al. *Ann Oncol*. 2017;28:3070-3075. **6.** Kim ES, et al. *J Thorac Oncol*. 2019;14:338-342.

Summary[1-6]

1. G/GEJ cancer is a complex and heterogenous disease with a need for novel targeted options[1]
2. FGFR2b is a member of the FGFR family of receptor tyrosine kinases, and its ligands bind with high specificity to FGFR2b[2]
3. FGFR2b protein overexpression (measured by IHC) can be independent of *FGFR2* gene amplification (measured using NGS/PCR)[3,4]
4. Optimization of tissue testing practices may support biomarker-informed clinical decision making[5,6]

FGFR, fibroblast growth factor receptor; FGFR2b, FGFR 2, isoform IIIb; G/GEJ, gastric or gastroesophageal junction; IHC, immunohistochemistry; NGS, next-generation sequencing; PCR, polymerase chain reaction.

1. De Mello RA, et al. *Am Soc Clin Oncol Educ Book*. 2018;38:249-261. **2.** Han N, et al. *Pathobiology*. 2015;82:269-279. **3.** Wainberg ZA, et al. Presented at: American Society of Clinical Oncology Gastrointestinal Cancer Symposium; January 15-17, 2021; Online Virtual Scientific Program. Abstract LBA160. **4**. Sato Y, et al. Novel biomarkers of gastric cancer: Current research and future perspectives. *J Clin Med*. 2023;12:4646. **5.** Aisner DL, et al. *Arch Pathol Lab Med*. 2016;140:1206-1220. **6.** Levy BP, et al. *Oncologist*. 2015;20:1175-1181.