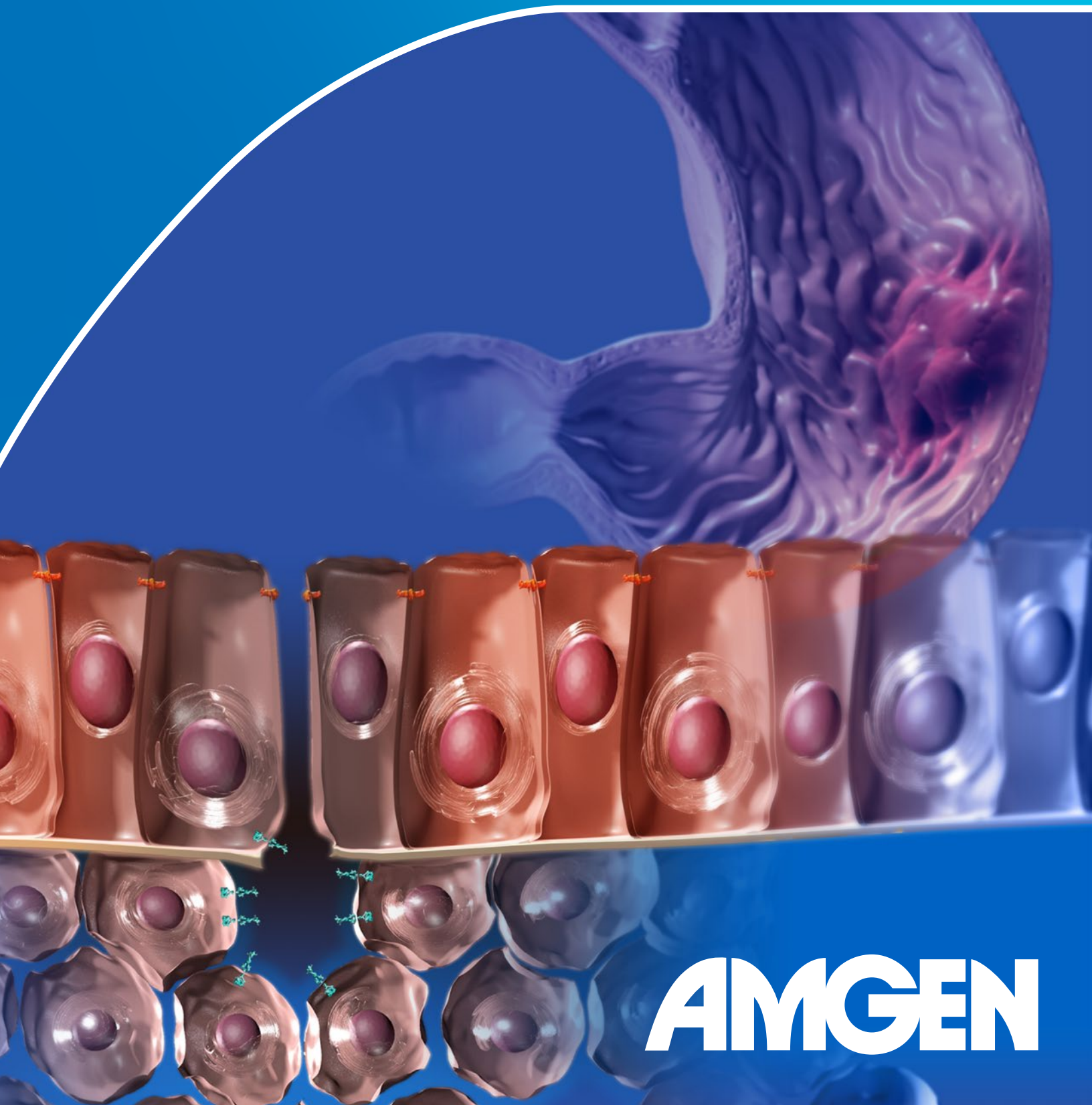
Gastric cancer and the evolving landscape of therapeutic targets



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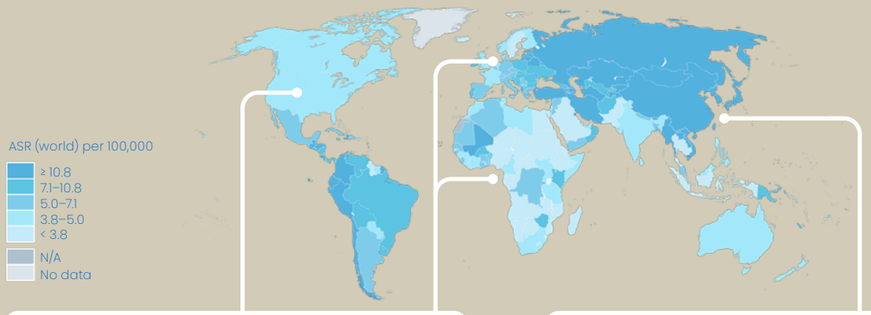
Gastric cancer is one of the most common malignancies, with varying incidence rates among regions[1]

Worldwide, there are approximately 1 million new cases of gastric cancer diagnosed each year, accounting for 5.7% of all new cancer diagnoses.[1,2,*] By 2040, this number is predicted to increase to 1.77 million.[3]

- Gastric cancer is the fifth most frequently diagnosed cancer, and incidence rates vary by region.[3]
  - In 2023, an estimated 26,500 people will be diagnosed with gastric cancer in the United States alone.[4]
- Gastric cancer is more prevalent in men than in women, with 66% of all cases occurring in men.[3]
- Although steady decreases in the incidence of gastric cancer have been noted globally, incidence rates in specific subpopulations have increased over the past decades.[3]
- Gastric cancer is a heterogenous disease characterized by the expression of certain proteins, including PD-L1 and CLDN18.2, RTKs (eg, FGFR2b and HER2), and growth factors (eg, VEGF).[5]

In countries where gastric cancer is more common, screening programs have aided in diagnosing more cases during the disease's early stages.[6] However, screening programs are available only in a limited number of countries.[2]

ESTIMATED AGE-STANDARDIZED INCIDENCE RATES (WORLD) FOR GASTRIC CANCER IN 2020, BOTH SEXES, ALL AGES[7]



- The incidence rates in Northern America and Europe are generally low (1.2% and 3.1%, respectively) and are consistent with rates observed across the African regions (2.9%).[8]

- Incidence rates are markedly elevated in Asia (8.6%), with the highest rates in the world observed in Japan (13.5%), the Republic of Korea (12.5%), and China (10.5%), in part due to the implementation of screening programs.[8]

*Based on GLOBOCAN 2022 data.[1]

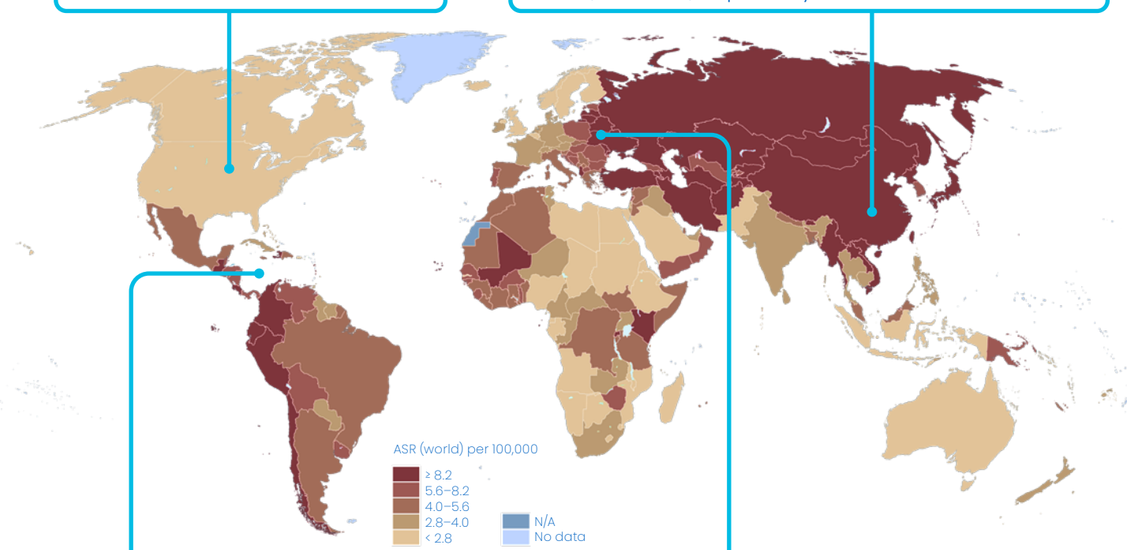
Gastric cancer is the fifth leading cause of cancer death worldwide[1]

In 2022, there were an estimated 659,853 deaths from gastric cancer, making it the fifth leading cause of cancer death in the world, with highest mortality rates observed in patients from Eastern Asia.[1]

ESTIMATED AGE-STANDARDIZED MORTALITY RATES (WORLD) FOR GASTRIC CANCER IN 2020, BOTH SEXES, ALL AGES[7]

- Mortality rates in the US and Northern America are both 1.9%.[8]
- In 2023, gastric cancer is estimated to cause 11,130 deaths in the United States.[4]

- The countries with the highest age-standardized gastric cancer mortality rates are in Asia, with a rate of 9.9%.[2,8]
- Even with early detection methods, the Republic of Korea, Japan, and China have elevated mortality rates of 8.5%, 11.0%, and 12.4%, respectively.[8,9]

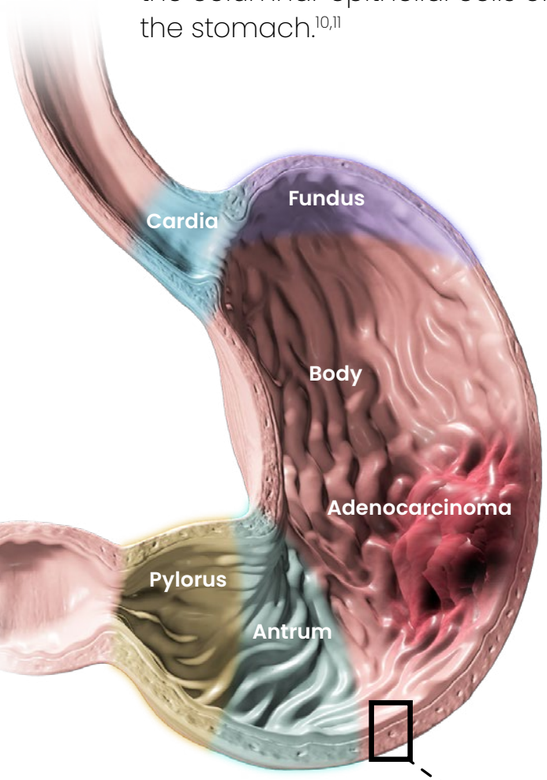


- Countries in Latin America and the Caribbean also have higher mortality rates, accounting for 7.5% of all cancer deaths.[8]
- Gastric cancer mortality rates in Brazil, Mexico, and Chile are 6.1%, 7.5%, and 11.6%, respectively.[8]

- The gastric cancer mortality rate in Europe is 5.0% and varies by country.[8]
  - Albania, 9.7%
  - United Kingdom, 2.4%
  - Russian Federation, 8.9%

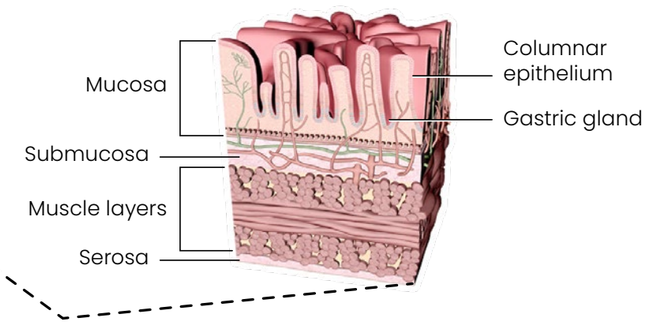
Pathophysiology of gastric cancer

Most gastric cancers (~ 90%) are adenocarcinomas, originating in the columnar epithelial cells of the stomach.[10,11]



Adenocarcinoma Classification Parameters	
Anatomical location[2,10]	**Frequency (%)**
Noncardia	~ 80
Cardia	~ 20
Histology[2,12]	**Frequency (%)**
Intestinal/well-differentiated	85–90
Diffuse/undifferentiated	10–15
Etiology[12]	**Frequency (%)**
Sporadic	90–95
Familial predisposition	5–10

The columnar epithelium and gastric glands composing the mucosa are prone to inflammation, known as gastritis, which can lead to peptic ulcers and, ultimately, gastric cancer.[2,4,13]



FACTORS INCREASING THE RISK OF GASTRIC CANCER

The development of gastric cancer is a complex, multistep process that involves environmental and genetic factors.[14,15]

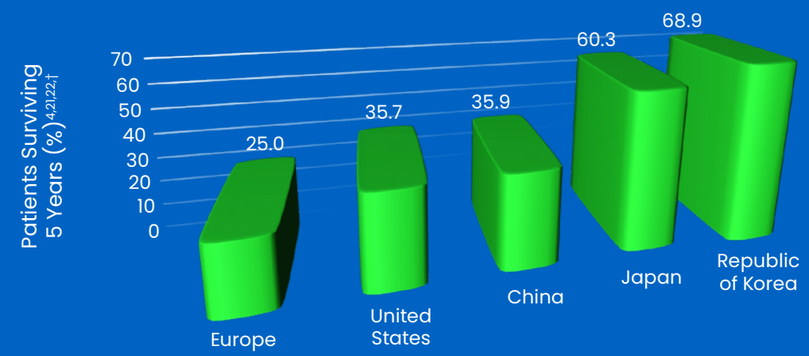
The main risk factor is *Helicobacter pylori* infection, with almost 90% of cases of noncardia gastric cancer attributed to this bacterium.[2] Other risk factors include:[16]

- Age and sex
- Epstein–Barr virus
- Alcohol consumption and tobacco smoking
- Obesity and diets rich in preserved foods and salt
- Genetic risk factors such as:[12,16,17]
  - Mutations in *CDH1, APC, EPCAM, IL12RB1*
  - Expression of PD-L1 and high MSI

Most patients with gastric cancer are diagnosed at an advanced stage, often with poor prognosis and low survival rates[18,19]

Globally, patients with gastric cancer have a 5-year survival rate of ~ 20%.[20,*] Treatment remains challenging, as many patients are diagnosed at an advanced stage and availability of treatments is limited.[12]

- The Europe-wide 5-year relative survival rate from 1999–2007 was 25%:[21]
  - Southern Europe reported the greatest 5-year survival outcomes (30%)
  - Eastern Europe reported the poorest survival outcomes (19%)
- In the United States from 2013 to 2019, the 5-year survival rate was 35.7% for all stages and 6.6% for patients with metastasized cancer.[4]
- The 5-year survival rates in Japan and the Republic of Korea are notably higher due to the early detection screenings that have led to the effective diagnosis of tumors at early stages:[20]



*Data from 195 countries and territories from 21 regions between 1990 and 2017.[20]
†Data collection for the US was from 2013 to 2019;[4] China, Japan, and Republic of Korea from 2010 to 2014;[22] Europe from 1999 to 2007.[21]

Biomarker testing in gastric cancer

Given the molecular heterogeneity of the disease, limited selective biomarkers, and available therapies, gastric cancers are challenging to diagnose and treat.[10]

Testing patients with metastatic gastric cancer for actionable and emerging biomarkers can provide an insight into a patient's likelihood of responding to targeted therapies.[23]

Biomarkers

Established[5]

Used to make clinical decisions for patient's response to targeted therapy

Emerging[5]

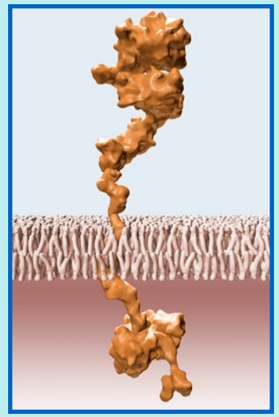
Used to identify new subsets of patients for developing targeted therapies

Established biomarkers in gastric cancer

1

HER2 Positivity[5]

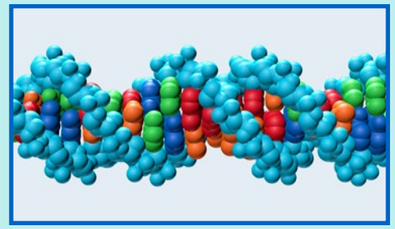
HER2 is a member of the human epidermal growth factor receptor family associated with tumor cell proliferation, adhesion, migration, and differentiation. Overexpression/amplification of HER2, detected by IHC/ISH, respectively, has been identified in 7%–53% of gastric cancer cases.



2

High MSI Status[24]

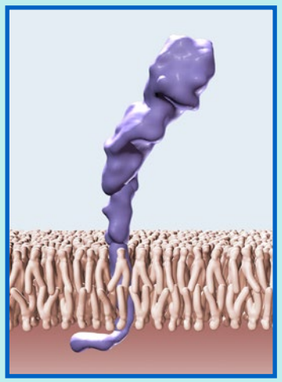
MSI is a subtype of gastric cancer which is characterized by mutations in the mismatch repair (MMR) gene and functional defects. MSI is detected by IHC, PCR, and NGS.[25] In advanced gastric cancer, the genotype for MMR deficiency accompanied by high MSI status presents in nearly 6% of patients.



3

PD-L1 Expression[5]

Some tumor cells express high levels of its ligand PD-L1 as an immune evasion mechanism because PD-1/PD-L1 interaction induces the inactivation of cytotoxic T cells and the downregulation of immune responses. PD-L1 expression is detected by IHC. Overexpression of PD-L1, determined by CPS, has been identified in 47%–82% of gastric cancer cases.



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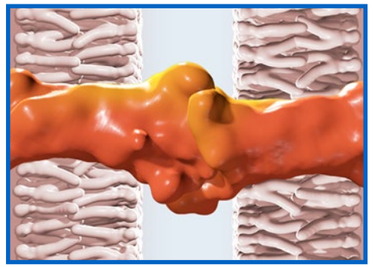
Key emerging biomarkers in gastric cancer

1

Claudin 18.2 (CLDN18.2)

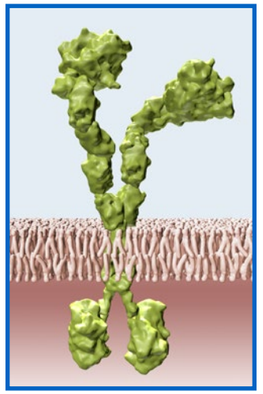
Claudins are a family of tight junction proteins establishing paracellular barriers, which control the flow of molecules between cells.[26] CLDN18.2 (tight junction molecule claudin-18 isoform 2) is highly expressed in the healthy stomach and is strictly confined to differentiated epithelial cells of the gastric mucosa.[27] It is detected by IHC.[5] CLDN18.2 is also detected in 14%–87% of primary gastric cancers.[5,28]



2

Mesenchymal-Epithelial Transition (MET)[5,29]

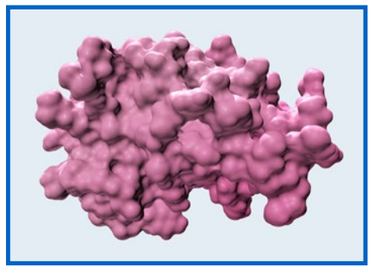
The MET proto-oncogene encodes an RTK protein called hepatocyte growth factor. MET activation regulates cell survival and proliferation. Most commonly, the MET pathway is activated in gastric cancer by protein overexpression, which can be detected by IHC, FISH, NGS, and ctDNA testing methods, and occurs in 50%–65% of cases. The MET proto-oncogene is expressed in tumor membrane and cytoplasm.



3

Matrix Metalloproteinases (MMP)[30]

MMPs are enzymes that belong to a family of Zn^{2+}-dependent endopeptidases that are closely associated with tumorigenesis, invasion, and metastasis. MMPs are secreted by tumor cells and lead to degradation of the extracellular matrix and cause cellular adhesions. Elevated MMP-7 expression, detected by IHC and SNP genotyping assays, is observed in ~ 70% of gastric cancer patients.



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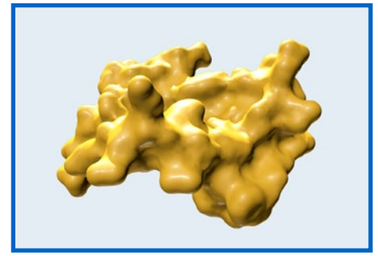
4

Dickkopf-related Protein (DKK-01)[31,32]

DKK-01 is a secretory protein and an important regulatory factor of the Wnt signaling pathway. DKK-01 is detected by IHC, ELISA, and qRT-PCR. High DKK-01 expression was noted in ~ 60% gastric cancer cases. It is mainly localized in the cytoplasm of tumor cells.



5

Fibroblast Growth Factor Receptor 2b (FGFR2b)

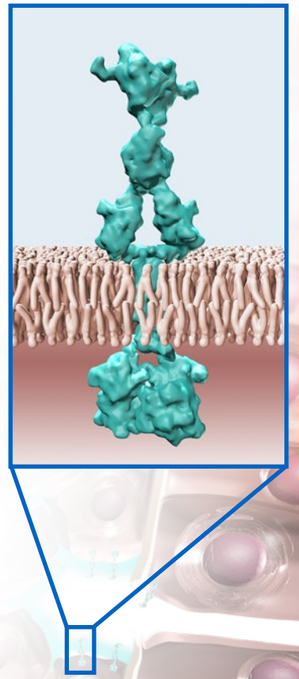
FGFR2b overexpression in gastric and GEJ cancers presents a potential target[33]

FGFR2b is a transmembrane RTK that normally participates in tissue repair, wound healing, and angiogenesis.[33]

The FGFR2b protein is a specific splice variant of the *FGFR2* gene. It belongs to the FGFR family of transmembrane RTKs, which are frequently dysregulated in many cancer types, resulting in enhanced angiogenesis and tumor cell proliferation.[34-37]

FGFR2b is preferentially expressed on the surface of epithelial cells, and its protein overexpression can be detected by IHC.[5,34]

FGFR2b protein overexpression, as detected by IHC, has been observed in approximately 20%–30% of patients with newly diagnosed advanced gastric and GEJ cancer.[38,*]

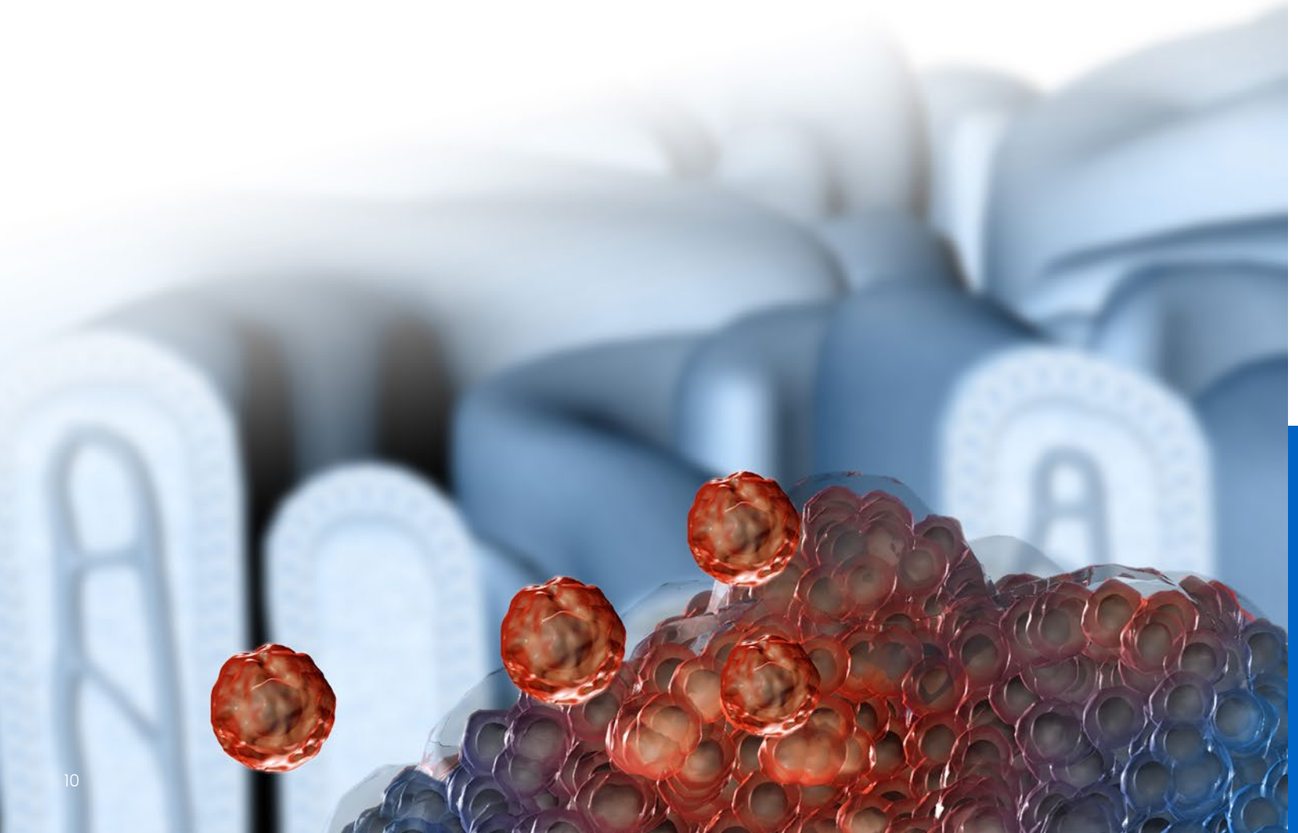


*FGFR2b prevalence may depend on disease state and cutoff point for IHC staining. Approximate range based on 910 prescreened patients for a phase 2 trial in locally advanced or metastatic gastric and GEJ cancer, of which 274 patients (30%) were prescreened positive for FGFR2b any 2+/3+ tumor cell staining by IHC, and on the 155 enrolled subjects, of which 96 subjects (62%) exhibited FGFR2b ≥10% 2+/3+ tumor cell staining by IHC.[38]

The images presented above are stocked images.

Key takeaways

- Gastric cancer is the fifth most commonly diagnosed cancer and the fifth leading cause of cancer death in the world. The incidence and mortality rates vary by region, with incidence rates increasing in some subpopulations.[1,3]
- Gastric cancer develops via a complex, multistep process, and is often diagnosed at an advanced stage, with limited available treatments resulting in poor patient outcomes.[14,15,18,19]
- Gastric cancer is a heterogenous disease characterized by the overexpression and mislocalization of certain proteins, including PD-L1, CLDN18.2, and RTKs (eg, FGFR2b, HER2), and growth factors (eg, VEGF).[5]



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ABBREVIATIONS:

APC, adenomatous polyposis coli; ASR, age-standardized rate; CDH1, cadherin-1; CLDN18.2, claudin-18 isoform 2; CPS, combined positive score; DKK, Dickkopf-related protein; ELISA, enzyme-linked immunosorbent assay; EPCAM, epithelial cell adhesion molecule; FGFR2b, fibroblast growth factor receptor 2, isoform IIIb; FISH, fluorescence in situ hybridization; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; IL12RB1, interleukin 12 receptor subunit beta 1; ISH, in situ hybridization; MET, mesenchymal-epithelial transition; MMP, matrix metalloproteinase; MMR, mismatch repair; MSI, microsatellite instability; N/A, not applicable; NGS, next-generation sequencing; PCR, polymerase chain reaction; PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; qRT-PCR, quantitative reverse transcriptase-PCR; RTK, receptor tyrosine kinase; VEGF, vascular endothelial growth factor.

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