
Discover Claudin18.2,
a novel biomarker in the advanced
gastric cancer landscape.
CLDN18.2
LET'S GET STARTED
CLDN18.2=Claudin18.2.
astellas

Despite recent advances, there are still critical needs to address in gastric/gastroesophageal junction (G/GEJ) cancers

In the United States, approximately 6% of patients with metastatic G/GEJ cancer survive 5 years post diagnosis.[1,2*†]

*US SEER 17 areas (2012-2018), gastric and esophageal cancers, distant stage.[1,2]
†SEER data do not have a separate classification for GEJ apart from esophageal cancer; therefore, true GEJ projections are unknown.[2]
‡Locally advanced (stage II and III) and metastatic (stage IV) G/GEJ cancer per tumor node metastases (TNM) classification as described in NCCN Guidelines.[4,5]
§Data from a retrospective analysis of electronic medical records of 3,850 eligible G/GEJ/esophageal adenocarcinoma patients that underwent first line therapy and were alive at 45 days after completion of first line therapy.[6]

TNM=tumor node metastases.

In 2023, an estimated 26,500 new cases of gastric cancer (62% advanced‡ stage) and **~21,600** new cases of esophageal† cancer (72% advanced‡ stage) will be diagnosed in the US.[1-3]

62-72% **ADVANCED STAGE DISEASE**

In the US, patients with advanced disease at diagnosis will likely have a **poor outcome,[4,5] and less than 50% will receive second-line therapy for mG/GEJ cancer.[6§]**

<50% **RECEIVE SECOND-LINE THERAPY**

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Despite recent advances, there are still critical needs to a

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therefore, true GEJ projections are unknown.[1,2]

As novel biomarkers emerge, they may reveal more opportunities to enhance care for advanced G/GEJ cancer

EMERGING BIOMARKERS

help identify previously undefined subsets of patients:

CLDN18.2, as a component of tight junctions, has a role in the regulation of permeability, barrier function, and polarity of epithelial layers[1-3]

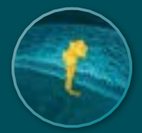
FGFR2b is a splice variant of FGFR2, a transmembrane signaling pathway that intermediates diverse cellular behaviours and processes, such as mitogenesis, differentiation, cell proliferation, angiogenesis, and invasion[4,5]

ESTABLISHED BIOMARKERS

are used to inform clinical decisions:

HER2 is associated with activation of downstream signaling that leads to uncontrolled cell-cycle progression, cell division and proliferation,motility, invasion, and adhesion[6]

MSI is characterized as somatic alterations in microsatellite sequences that are associated with genomic instability[4,7] MSI occurs when the DNA **MMR** system does not function appropriately[7]



PD-L1 can bind to the immune checkpoint receptor PD-1 (programmed death cell protein 1) which allows tumors to escape immune surveillance[8]

CLDN18.2=Claudin18.2; **FGFR2b**=fibroblast growth factor receptor 2, isoform IIIb; **HER2**=human epidermal growth factor receptor 2; **MMR**=mismatch repair; **MSI**=microsatellite instability; **PD-L1**=programmed death-ligand 1.

Tap each image above to learn more

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As novel biomarkers emerge, they may reveal more

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CLDN18.2=Claudin18.2, isoform IIIb; FGFR2b=fibroblast growth factor receptor 2b; HER2=human epidermal growth factor receptor; MMR=mismatch repair; MSI=microsatellite instability; PD-L1=programmed death-ligand 1;.

CLDN18.2

(Claudin18.2)

CLDN18.2 is an emerging biomarker that may help you learn more about your patients with advanced G/GEJ cancer[1]

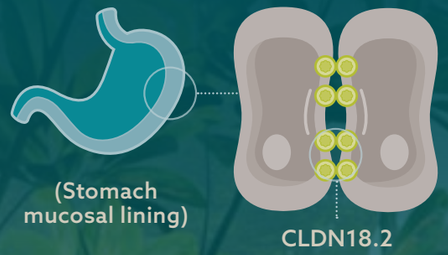
Claudins are a family of transmembrane proteins[2]

Claudins are present throughout the body, but CLDN18.2 is the dominant CLDN18 isoform in gastric tissue[2,3]

CLDN18.2 is typically buried in tight junctions.

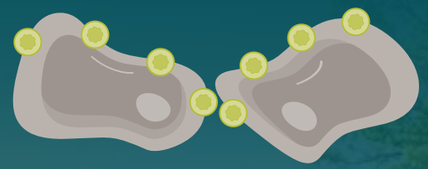
Preclinical data have shown that CLDN18.2 may become more exposed as gastric tumors develop.[1,2]

CONFINED IN HEALTHY TISSUE



In normal gastric mucosa, CLDN18.2 is typically buried within tight junctions.[1,2]

RETAINED AND EXPOSED IN MALIGNANT TRANSFORMATION



CLDN18.2 is often retained during malignant transformation. CLDN18.2 may be more exposed when cell polarity disruptions and structure loss occur.[1,2,4]

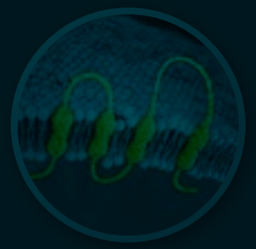
MAINTAINED IN METASTATIC PROGRESSION

CLDN18.2 may also be localized in lymph node metastases of gastric adenocarcinoma as well as other distant metastatic sites.[2,5-7]

The information provided above is based on the current understanding of data.

CLDN18.2 expression may also be observed in esophageal adenocarcinoma, pancreatic adenocarcinoma, non-small cell lung cancer, and ovarian mucinous adenocarcinoma.[2]

REFERENCES



CLDN18.2 is an emerging biomarker that may help you learn more

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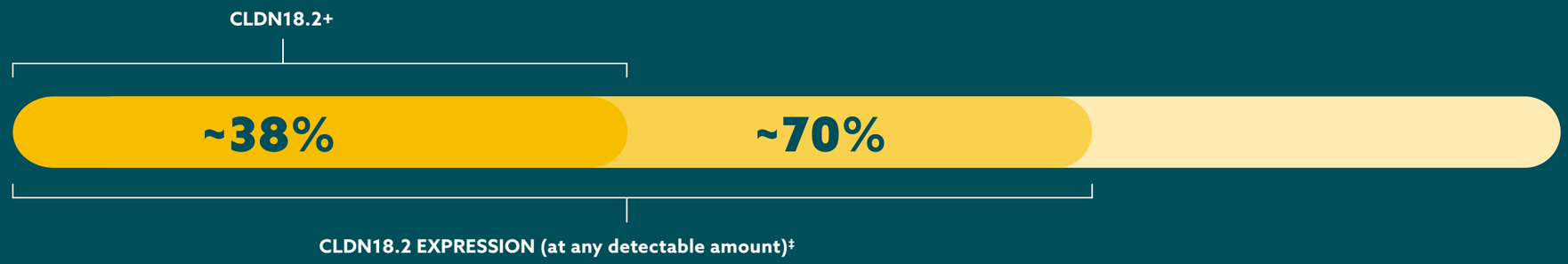
...astric tissue[3,4]

CLDN18.2 may be expressed when tumors develop in esophageal, pancreatic, lung, and ovarian tissues as well[3]

Detecting the presence of CLDN18.2 identifies a previously undefined patient population

While approximately 70% of advanced G/GEJ cancers express CLDN18.2 (at any detectable amount),[1*] two recent studies have shown that **approximately 38%** of patients with locally advanced unresectable or mG/GEJ cancer are **CLDN18.2 positive** (≥75% of tumor cells demonstrating moderate to strong membranous CLDN18 staining by IHC).[2,3†]



*Data from a retrospective analysis of 350 Caucasian patients with advanced G/GEJ cancer.[1]
†Data from 2 global randomized Phase 3 studies: the first study included 2,403 assessable patients, of which 922 were CLDN18.2 positive; and the second study which included 2,104 assessable patients, of which 808 were CLDN18.2 positive.[2,3]
‡Any detectable amount: moderate to strong membranous CLDN18 staining by IHC in any percentage of tumor cells.[1]

PREVALENCE OF ESTABLISHED AND EMERGING BIOMARKERS

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Detecting the presence of CLDN18.2 identifies a previously

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*Data from a retrospective analysis of 350 Caucasian patients with locally advanced and mG/GEJ cancer.[1]
†Data from a global randomized Phase 3 study involving 565 patients with locally advanced unresectable and mG/GEJ cancer.[2]

CLDN18.2 is highly prevalent among biomarkers for advanced G/GEJ cancer.

Biomarker prevalence estimates from select studies are reported below. Prevalence data can vary among studies due to tumor heterogeneity, differences in patient population, clinical trial methodology, and diagnostic assays used . Positivity thresholds also vary by study.[1-7]

EMERGING BIOMARKERS

CLDN18.2[1,2] (positive)*	FGFR2b[3] (positive)†
38%	30%

ESTABLISHED BIOMARKERS

PD-L1[4,5] (variable due to multiple factors)‡	HER2[6] (positive)	MSI[7] (MSI-high)
CPS ≥1: 67-73% CPS ≥5: 29-31% CPS ≥10: 16-18%	22%	4%

CPS=combined positive score.
*CLDN18.2 positivity: ≥75% of tumor cells demonstrating moderate to strong membranous CLDN18 staining by IHC.[1,2]
†FGFR2b positivity: FGFR2b overexpression (IHC 2+/3+ any amount of tumor cells) and/or FGFR2 gene amplification by ctDNA (NGS 1.5x increase in FGFR2).[3]
‡PD-L1 prevalence at various CPS thresholds is still being explored. Data are from a randomized controlled trial and a real-world retrospective medical records study.[4,5]

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CLDN18.2 is highly prevalent among mG/GEJ biomarkers.

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CLDN18.2 is detected via IHC, as is standard with many other biomarkers[1-4]

EMERGING BIOMARKERS

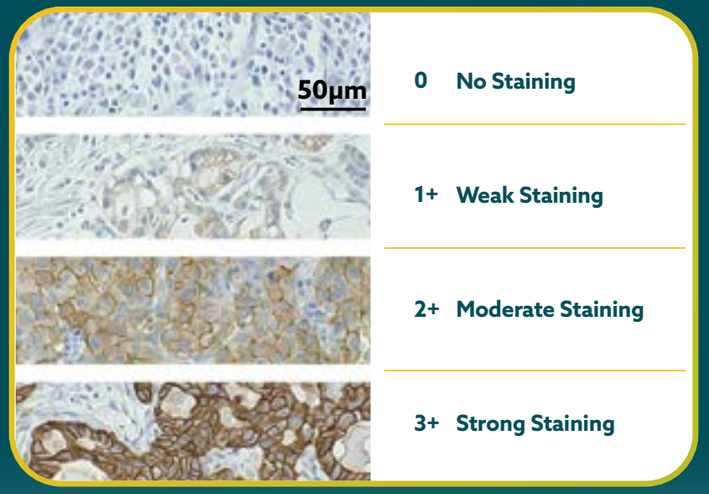
CLDN18.2: IHC[1,2]	FGFR2b: IHC, NGS (ctDNA)[5*]

ESTABLISHED BIOMARKERS

PD-L1: IHC[6,7†]	HER2: IHC, ISH, NGS[3,6,7‡]	MMR/MSI: IHC, PCR/NGS[6,7]

IHC=immunohistochemistry; **ctDNA**=circulating tumor DNA; **ISH**=in situ hybridization; **NGS**=next generation sequencing; **PCR**=polymerase chain reaction.
*FGFR2b protein overexpression assessed by IHC; FGFR2 gene amplification assessed using ctDNA by NGS.[5]
†Varying diagnostic assays.[8]
‡Other ISH methods (**FISH**=fluorescent ISH; **SISH**=silver ISH; **CISH**=chromogenic ISH; **DDISH**=dual-color dual-hapten ISH).[3]

IHC scoring for CLDN18 in G/GEJ cancer is performed based on membrane staining intensity and percent of positive tumor cells.[1,2,9]



CLDN18.2 positivity is defined as ≥75% of tumor cells demonstrating moderate to strong membranous CLDN18 staining by IHC.[1,2]

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Initial diagnostic panels with biomarker testing may lead to more comprehensive patient profiles and more informed clinical decisions

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Gastric Cancer and Esophageal and Esophagogastric Junction Cancers* support using biomarkers to help map the path forward for patients.[1,2†]

- Biomarker testing has an important role in the diagnosis, classification, and molecular characterization of G/GEJ cancer
- The implementation of molecular testing has had a significant impact on clinical practice and patient care

The NCCN Guidelines® recommend[1,2]:

- Testing for all established biomarkers (HER2, MSI, PD-L1) at diagnosis if metastatic cancer is documented or suspected
- The use of IHC/ISH/targeted PCR should be considered first, followed by additional NGS testing as appropriate

*In adenocarcinomas of unresectable locally advanced, locally recurrent or metastatic disease of esophageal and esophagogastric junction cancers.[2]
†This is a summary of relevant portions of the NCCN Guidelines. Please see the full NCCN Guidelines for Gastric Cancer and Esophageal and Esophagogastric Junction Cancers at NCCN.org.[1,2]

REFERENCES

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Biomarker testing provides more insight into advanced G/GEJ cancer as more biomarkers are discovered

Standard IHC staining methods can detect a wide range of emerging and established biomarkers

- IHC can detect CLDN18.2, FGFR2b, PD-L1, HER2, MMR[1-5]
- Other testing methods often focus on specific biomarkers (ctDNA for FGFR2, ISH/NGS for HER2, and PCR/NGS for MSI)[3-6]*

*The use of IHC/ISH/targeted PCR should be considered first, followed by additional NGS testing as appropriate.[4,5]

According to recent studies, biomarker testing has revealed a high prevalence of emerging biomarkers

- Approximately 38% of patients with locally advanced unresectable or mG/GEJ cancer are CLDN18.2 positive[1,2]
- 30% of advanced G/GEJ cancers observed FGFR2b positivity[3]*

Prevalence of established biomarkers have been reported throughout various studies as:

- HER2 positivity in 22% of advanced G/GEJ cancers[7]*
- MSI-H in 4% of advanced G/GEJ cancers[8]*
- PD-L1 at several positivity thresholds: 67-73% CPS ≥1, 29-31% CPS ≥5, and 16-18% CPS ≥10[9,10]*

*Data from select studies. Prevalence data can vary among studies due to tumor heterogeneity, differences in patient populations, clinical trial methodology, and diagnostic assays used. Positivity thresholds may vary by study.[3,7-10]

As biomarker research continues, it expands our view of the patient population, reveals more information about the advanced G/GEJ cancer landscape, and helps inform clinical decisions.

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Biomarker testing provides more insight into mG/GEJ cancer

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* Locally advanced (stage II and III) and metastatic (stage IV) G/GEJ cancer per TNM staging classification as described in NCCN Guidelines®.[4,5]
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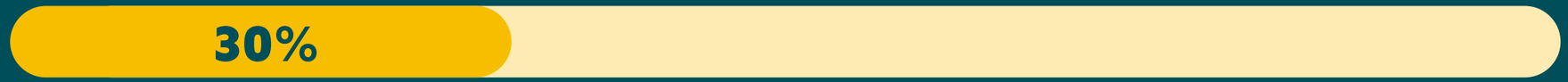
§Data from a global randomized Phase 3 study involving 565 patients with locally advanced unresectable and mG/GEJ cancer.[3]
‖CLDN18.2 positivity is defined as moderate to strong membranous CLDN18 staining by IHC in ≥75% tumor cells.[3]

FGFR2b (fibroblast growth factor receptor 2, isoform IIIb)

- FGFR2b participates in angiogenesis and cell proliferation through FGFR signaling pathways[1,2]
- FGFR2 is a receptor tyrosine kinase that has a role in normal cell development[3]
- The splice variant FGFR2b is also expressed in various other types of epithelial cells where tumors may begin to grow (including pancreatic, breast, endometrial, cervical, lung, and colorectal cancers)[3,4]
- FGRF2b may be associated with higher T stage (size of the tumor and any spread into nearby tissue) and higher N stage (extent of nodal metastasis)[2,5]

FGFR2b positivity can be observed in 30% of advanced G/GEJ cancers.[6]*



FGFR2b positivity: FGFR2b overexpression (IHC 2+/3+ any amount of tumor cells) and/or FGFR2 gene amplification by ctDNA (NGS 1.5x increase in FGFR2).

Detecting **FGFR2b** can be done with the **following tests**[6]:

- FGFR2b overexpression using IHC
- FGFR2 gene amplification using ctDNA by NGS

*Data from select studies.[6]

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FGFR2b (fibroblast growth factor receptor 2b)

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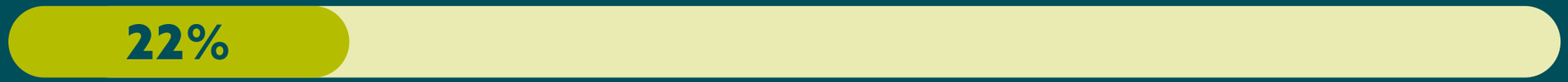
HER2 (human epidermal growth factor receptor 2)

- HER2 is a receptor-tyrosine kinase that is overexpressed and/or amplified in advanced G/GEJ cancer[1]
- HER2 is a proto-oncogene involved in signaling pathways, which leads to cell growth and differentiation[2]
- Studies have shown HER2 is present in several cancers, including colorectal, ovarian, prostate, and lung tumors[2]
- When HER2 is overexpressed and/or amplified, it can lead to uncontrolled cell growth and tumorigenesis[3]
  - However, the mechanisms that lead to gene amplification remain largely unknown[4]

HER2 positivity has been reported in 22% of advanced G/GEJ cancers.[3]*



HER2 positivity: overexpression (IHC3+) and/or gene amplification (FISH-positive)

Detection of HER2 may be done with **IHC, NGS,**† and **ISH methods.**[5,6]

- Guidelines recommend starting with IHC; followed by ISH (FISH, SISH, CISH, and DDISH) only when IHC expression is 2+ (equivocal)[2,5,6]
- Positive (3+) or negative (0 or 1+) IHC results do not require further testing via ISH[5,6]
- HER2 scoring criteria in gastric cancer differ from those in breast cancer[2,3]
- Overexpression or amplification of HER2 is more common in patients with intestinal histology[3]

*Data from select studies.[3]
†IHC/ISH should be considered first, followed by additional NGS testing as appropriate.[5,6]

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HER2 (human epidermal growth factor receptor 2)

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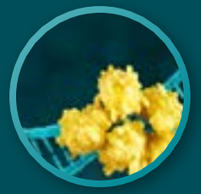

MSI (microsatellite instability)

Microsatellites are **repeated sequences** of nucleotides in DNA.[1]

- Microsatellite instability (MSI) is caused when the DNA mismatch repair system (MMR) does not function appropriately[1]
  - This loss prevents normal repair and correction of DNA, allowing mismatches to occur[1]
  - The MMR proteins are the most frequently mutated genes in cancer[1]
  - Tumors with ≥30% expression of unstable microsatellites are considered MSI-High; 10-29% expression is considered MSI-Low[2]
  - MSI is associated with genomic instability and increased susceptibility to tumor development[2]
- MSI is found most often in colorectal, gastric, and endometrial cancers, but may also be found in many other types of cancer[1]

MSI-High has been reported in 4% of advanced G/GEJ cancers.[3]*

Detection of MSI and MMR is typically assessed with **various methods.**[4,5]

- MSI gene expression can be detected via PCR-based molecular testing and NGS
- MMR protein expression can be analyzed via IHC

*Data from select studies.[3]

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REFERENCES

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PD-L1 (programmed death-ligand 1)

- PD-L1 is a transmembrane protein that may be expressed on various tumor cells and/or immune cells[1]
- When bound to PD-1, PD-L1 acts as a T-cell inhibitory molecule, leading to immune cell evasion and subsequent tumor cell survival[1]
- PD-L1 expression has been detected in various tumors, including lung, colon, ovarian, and gastric cancers[2]
- However, the cellular process of expression may not always be the same throughout the body[3]
  - Various studies have shown discordant levels of PD-L1 in the primary tumor vs metastatic lesions[3]

Prevalence of PD-L1 has been reported for several positivity thresholds throughout various studies:[4,5]*

67-73% — CPS ≥1

29-31% — CPS ≥5

16-18% — CPS ≥10

PD-L1 prevalence at various CPS thresholds is still being explored. Data are from a randomized controlled trial and a real-world retrospective medical records study.[4,5]

- The variations in prevalence may be due to several factors, such as tumor heterogeneity and clinical trial methodology (including differences in patient population, staining techniques, scoring algorithms, and diagnostic assays)[3,6]
- Expression levels may also vary during disease progression, as PD-L1 is impacted by changes in immune response[3]

CPS=combined positive score.
*Data from select studies.[4,5]

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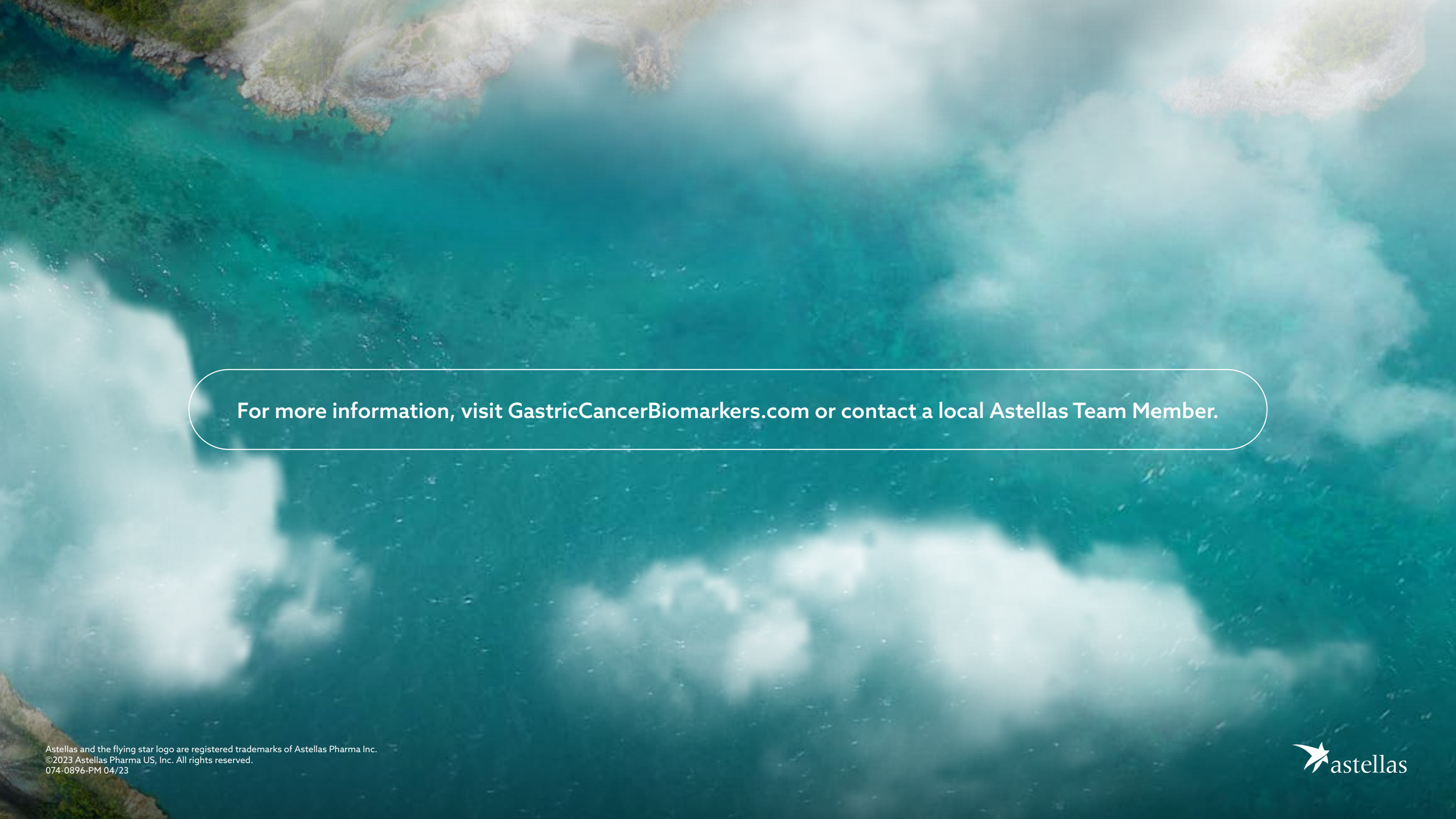
CPS=combined positive score.



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