



**CHALLENGING**  
**CASES**  
*Gastric/GEJ Cancer*

Prepared by: Cornerstone Specialty Network

***Challenging Cases conducted: July 22, 2025, July 28, 2025, August 14, 2025, October 1, 2025, October 6, 2025***

# Participating Practices

## **Challenging Cases In... Gastric/ GEJ Cancer**

**Program conducted:  
July–October 2025**

*Note: Aggregated results and high-level summary based on 5 practices (≤33 HCPs) and do not necessarily reflect the views and opinions of the moderator or Cornerstone Specialty Network unless otherwise stated. Clinical data, NCCN Guidelines, and FDA approvals current at time of presentation.*

- **New Mexico Cancer Center (n=5)** **July 22, 2025**
- **Utah Cancer Specialists (n=8)** **July 28, 2025**
- **Cancer Center of Kansas (n=6)** **August 14, 2025**
- **Northwestern Medicine (n=7)** **October 1, 2025**
- **Highlands Oncology (n=7)** **October 6, 2025**

# Overall Program Impact and Future Considerations

Clinicians reported routinely testing CLDN18.2 and other biomarkers for 1L metastatic Gastric/GEJ cancer with no consistent vendor; Zolbetuximab used first-line in most CLDN18.2-positive patients while immunotherapy is preferred by some especially for PD-L1-positive or MSI-high tumors due to better tolerability and durable responses; most remain cautious due to Zolbetuximab's acute infusion related nausea, infusion complexity, and payer restrictions with treatment decisions driven more by toxicity management as well as prescriber and patient comfort/QoL

- **CLDN18.2 Testing:** Most clinicians are routinely testing for CLDN18.2 via IHC, often through NGS panels from third-party labs; turnaround times vary from 1–4 weeks
- **PD-L1 and Other Biomarkers:** PD-L1 positivity is generally considered qualitatively (positive/negative) rather than by CPS score; MSI-high tumors favor immunotherapy over Zolbetuximab
- **Treatment Sequencing:** Zolbetuximab is used 1L in CLDN18.2-positive patients to meet insurance approval but often IO therapy is utilized based on greater comfort, lower toxicity, and durable long-term responses
- **Toxicity Management:** Acute nausea and vomiting are concerns in early cycles of Zolbetuximab; strategies include slower infusions, split dosing, premedications, and patient education
- **Clinical Decision Drivers:** Decisions are influenced by toxicity profile, long-term response, and payer constraints than biomarker testing results
- **Practical Challenges:** Access and timing of testing, payer restrictions, and the need for alternative chemo backbones in 2L setting limit broader Zolbetuximab adoption
- **Recommended actions:** Educational initiatives emphasizing practical strategies for toxicity management, optimal sequencing with chemotherapy and immunotherapy, and timely biomarker testing to overcome real-world adoption barriers

# *Challenging Cases in Gastric/GEJ Cancer*

## Gastric / GEJ Cancer

Patient Case: 1L metastatic untreated, inoperable

- What is the optimal treatment strategy for patients in the 1L metastatic setting?
- How does biomarker testing results impact your treatment decisions?
  - CLDN18.2, PD-L1, HER2, MMR or MSI
- Awareness of clinical trial data?

# 1st-line Metastatic Therapy Decision

## *Patient History*

### *66-year-old male*

- *4-month history of decreased appetite, bloating, and abdominal discomfort*
- *Unintentional weight loss*
- *High blood pressure*
- *Diabetes mellitus*
- *No family history*

## *Metastatic Diagnosis*

*CBCs: Hgb 9.2 g/dL, PLT 104 x 10<sup>9</sup>/L*

*Endoscopy revealed mass in stomach, confirmed by abdominal CT: 5.1 cm mass with indistinct margins*

*ECOG PS: 1*

*Microsatellite stable (MSS)*

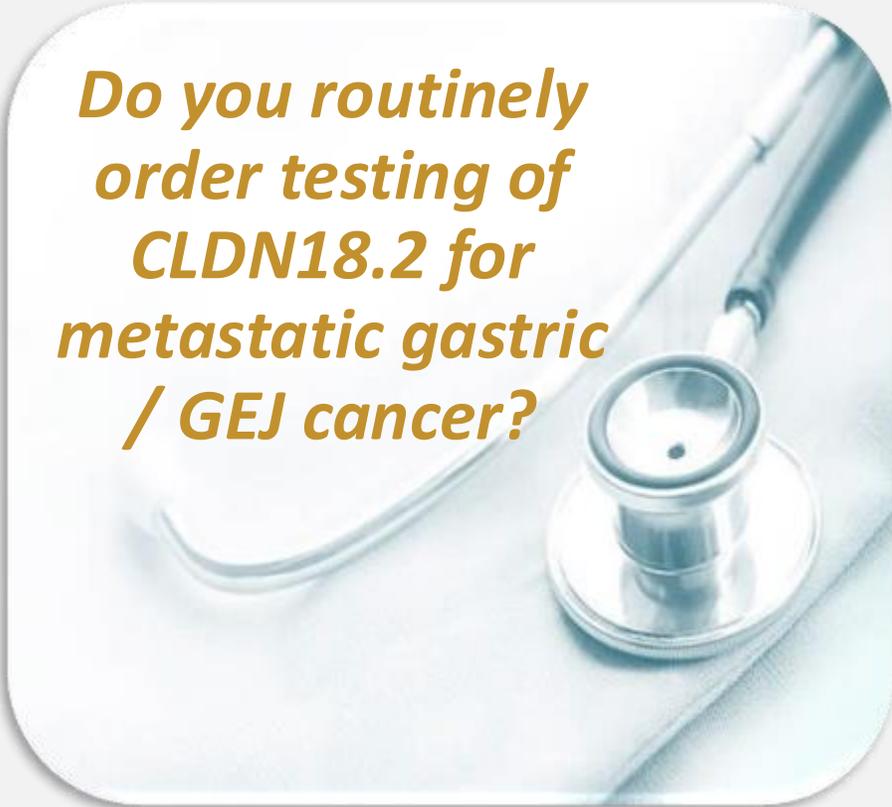
*HER2 negative (IHC 1+)*

*CLDN18.2 positive*

*PD-L1 CPS score  $\geq 1$*

*Stage IV disease*

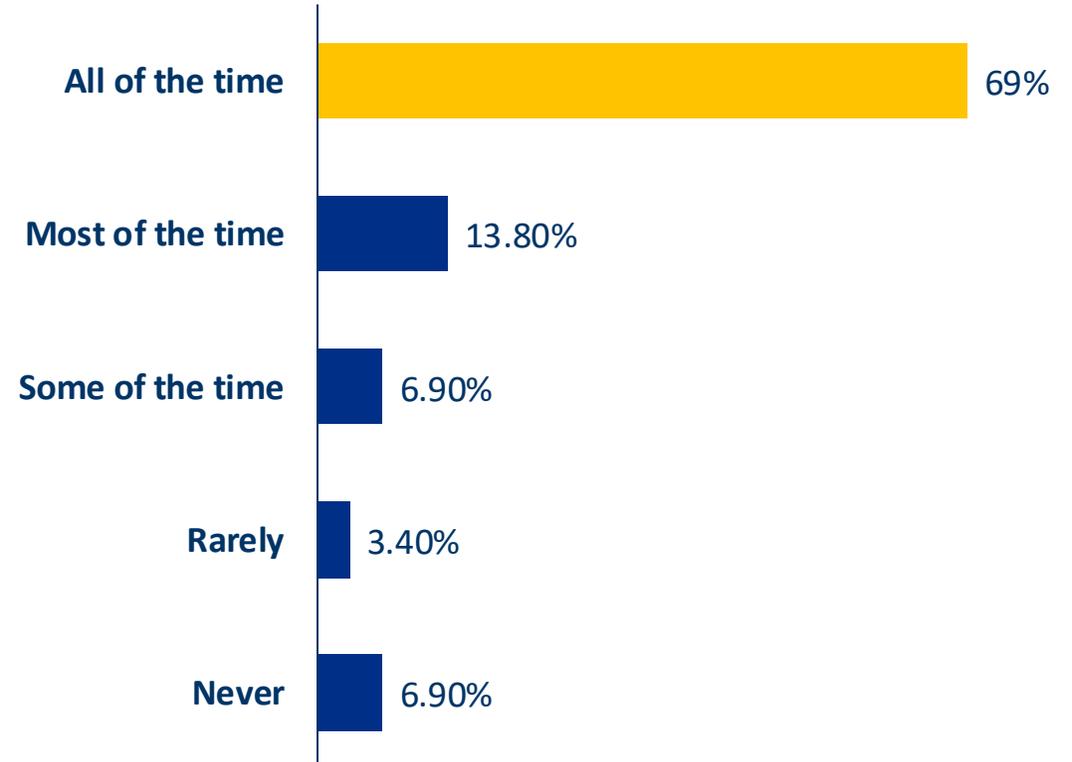
*Do you routinely order testing of CLDN18.2 for metastatic gastric / GEJ cancer?*





# ARS Results from HCP Participants

**Do you routinely order testing of CLDN18.2 for metastatic gastric / GEJ cancer?**



PRINCIPLES OF PATHOLOGIC REVIEW AND BIOMARKER TESTING

**Assessment of Positivity of Claudin 18 Isoform 2 (CLDN18.2) in Gastric Cancer<sup>5-7</sup>**

- For patients with untreated inoperable locally advanced, recurrent, or metastatic adenocarcinoma of the stomach for whom zolbetuximab therapy is being considered

**Table 4: Immunohistochemical Criteria for Assessing CLDN18.2 Expression in Gastric Cancer**

CLDN18.2 Assessment	Biopsy or Surgical Specimen Expression Pattern by IHC
Positive	≥75% viable tumor cells demonstrating moderate to strong membrane CLDN18.2 staining (2+ or 3+ intensity)
Negative	<75% viable tumor cells demonstrating moderate to strong membrane CLDN18.2 staining

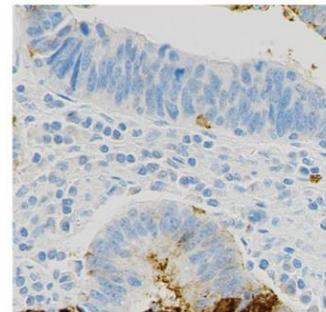
**Next-Generation Sequencing (NGS):**

- At present, several targeted therapeutic agents (GAST-F) have been approved by the FDA for use in gastric cancer. **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. The list of targeted biomarkers includes:

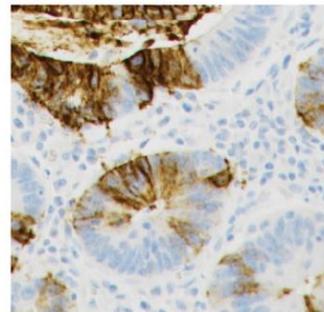
- ▶ HER2 overexpression/amplification
- ▶ PD-L1 expression
- ▶ MSI
- ▶ **CLDN18.2**
- ▶ TMB
- ▶ NTRK gene fusion
- ▶ RET gene fusion
- ▶ BRAF V600E mutation

*CLDN18.2 status is evaluated using both membranous staining intensity and percentage of viable tumor cells stained*

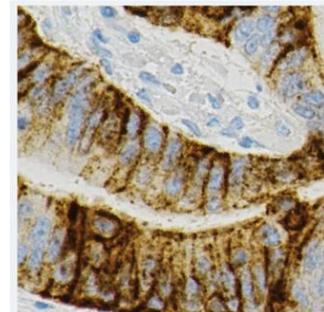
**CLDN18.2  
is not  
assessable  
with NGS**



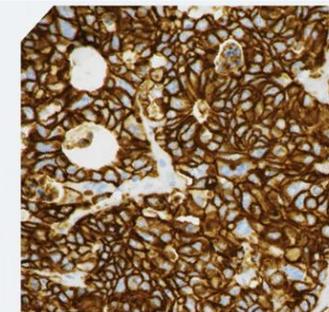
No staining



Weak staining



Moderate staining



Strong staining

# 1st-line Metastatic Therapy Decision

## Patient History

### 66-year-old male

- 4-month history of decreased appetite, bloating, and abdominal discomfort
- Unintentional weight loss
- High blood pressure
- Diabetes mellitus
- No family history

## Metastatic Diagnosis

CBCs: Hgb 9.2 g/dL, PLT 104 x 10<sup>9</sup>/L

Endoscopy revealed mass in stomach, confirmed by abdominal CT: 5.1 cm mass with indistinct margins

ECOG PS: 1

Microsatellite stable (MSS)

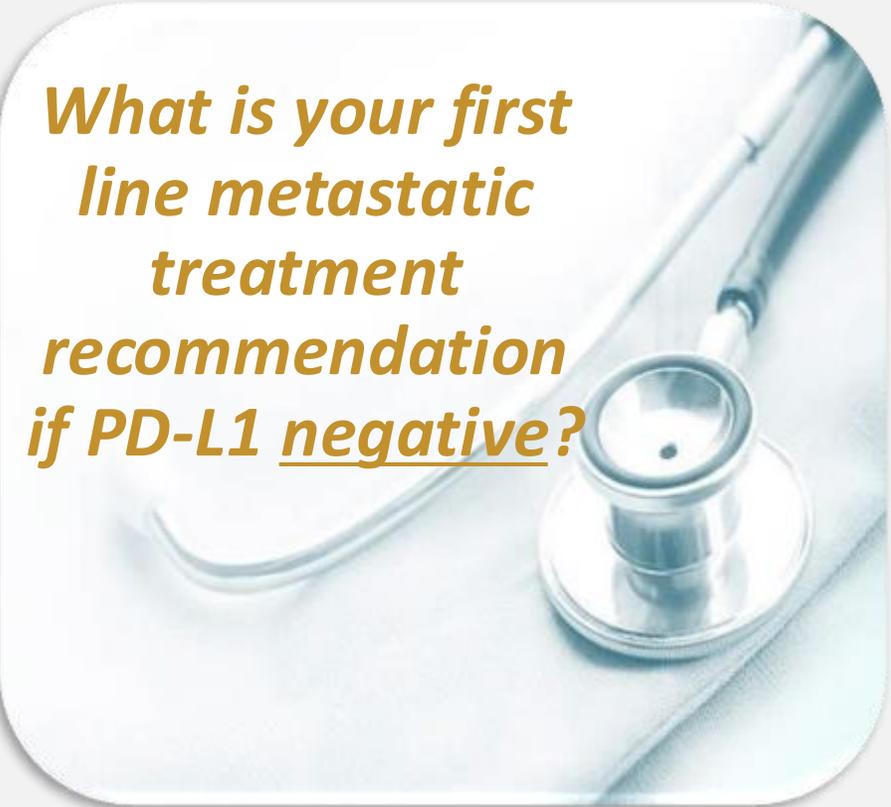
**HER2 negative (IHC 1+)**

**CLDN18.2 positive**

**PD-L1 CPS score <1 (negative)**

**Stage IV disease**

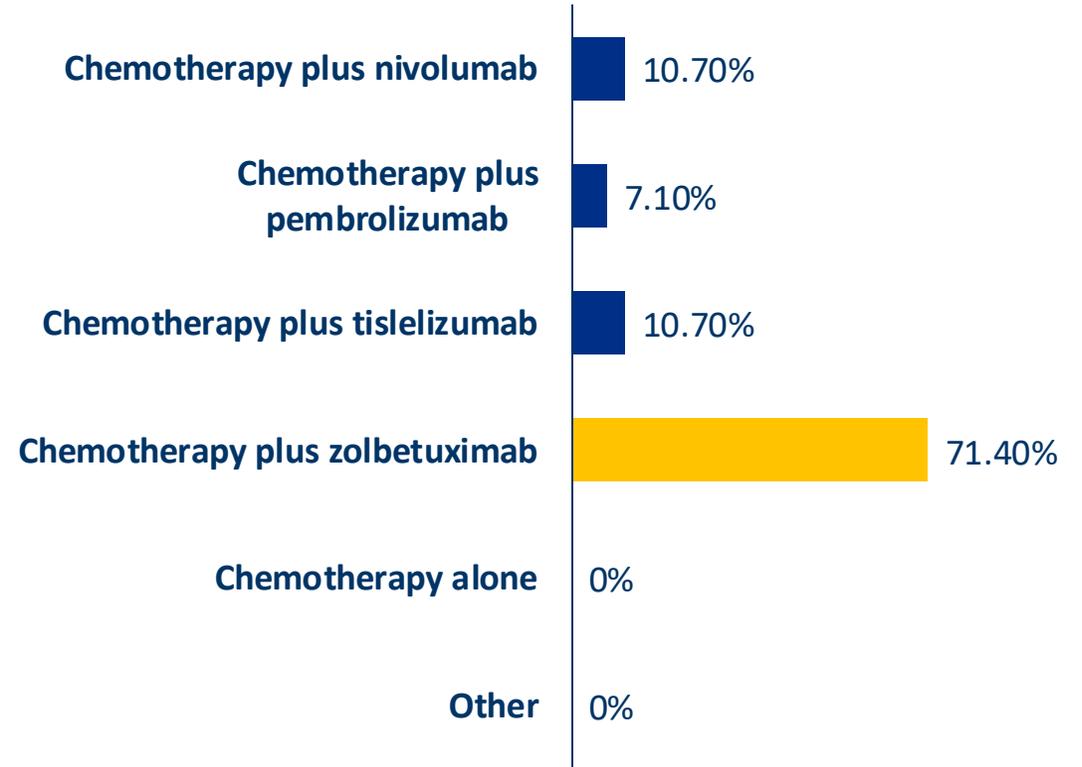
**What is your first line metastatic treatment recommendation if PD-L1 negative?**





# ARS Results from HCP Participants

**What is your first line metastatic treatment recommendation if HER2 negative, PD-L1 negative, CLDN18.2 positive gastric / GEJ cancer?**



# 1st-line Metastatic Therapy Decision

## Patient History

### 66-year-old male

- 4-month history of decreased appetite, bloating, and abdominal discomfort
- Unintentional weight loss
- High blood pressure
- Diabetes mellitus
- No family history

## Metastatic Diagnosis

CBCs: Hgb 9.2 g/dL, PLT  $104 \times 10^9/L$

Endoscopy revealed mass in stomach, confirmed by abdominal CT: 5.1 cm mass with indistinct margins

ECOG PS: 1

Microsatellite stable (MSS)

**HER2 negative (IHC 1+)**

**CLDN18.2 positive**

**PD-L1 CPS score  $\geq 5$  (positive)**

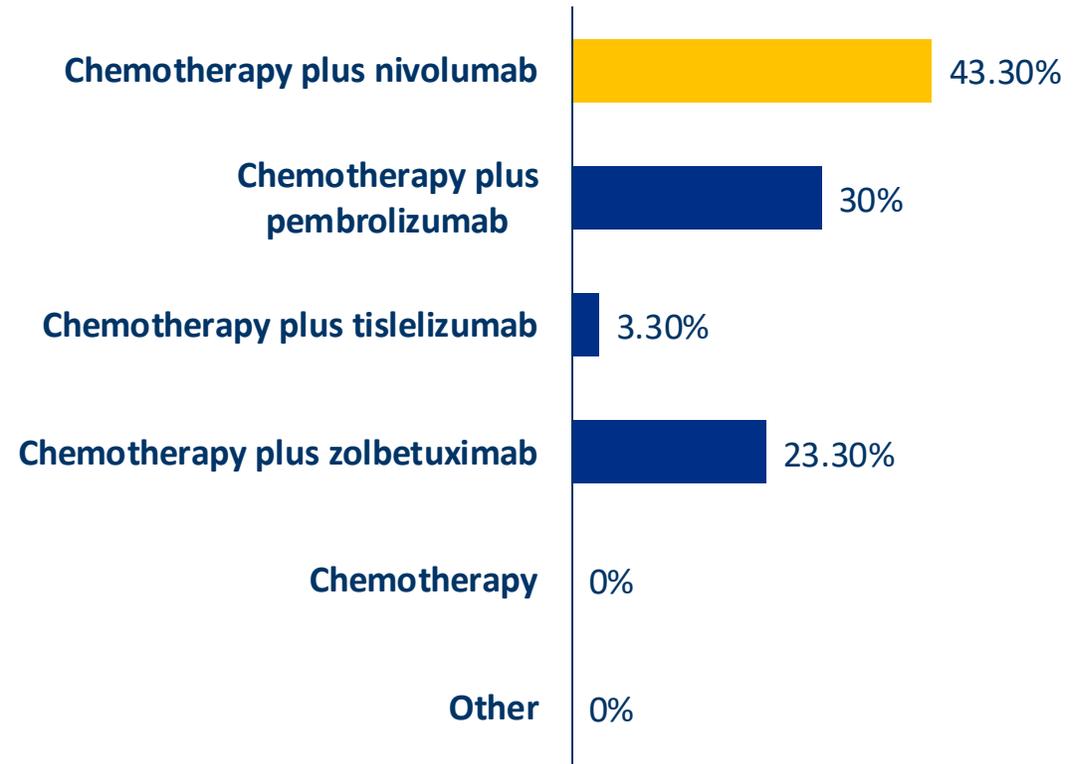
**Stage IV disease**

**What is your first line metastatic treatment recommendation if PD-L1 positive?**



# ARS Results from HCP Participants

**What is your first line metastatic treatment recommendation *if HER2 negative, PD-L1 positive, CLDN18.2 positive gastric / GEJ cancer?***





*Is NCCN Guideline category by PD-L1 status impactful?*

*Do you consider PD-L1 in more binary terms of positive and negative?*

PRINCIPLES OF SYSTEMIC THERAPY

**Systemic Therapy for Unresectable Locally Advanced, Recurrent, or Metastatic Disease (where local therapy is not indicated)**

<p><b>First-Line Therapy</b></p> <ul style="list-style-type: none"> <li>• Oxaliplatin is preferred over cisplatin due to lower toxicity.</li> </ul>
<p><b>Preferred Regimens</b></p> <ul style="list-style-type: none"> <li>• HER2 overexpression positive<sup>b</sup> <ul style="list-style-type: none"> <li>▶ Fluoropyrimidine (fluorouracil<sup>a</sup> or capecitabine), oxaliplatin, and trastuzumab</li> <li>▶ Fluoropyrimidine (fluorouracil<sup>a</sup> or capecitabine), oxaliplatin, trastuzumab, and pembrolizumab for PD-L1 CPS ≥1 (category 1)<sup>c,f,15-16</sup></li> <li>▶ Fluoropyrimidine (fluorouracil<sup>a</sup> or capecitabine), cisplatin, and trastuzumab (category 1)<sup>17</sup></li> <li>▶ Fluoropyrimidine (fluorouracil<sup>a</sup> or capecitabine), cisplatin, trastuzumab, and pembrolizumab for PD-L1 CPS ≥1 (category 1)<sup>c,f,15-16</sup></li> </ul> </li> <li>• HER2 overexpression negative<sup>d</sup> <ul style="list-style-type: none"> <li>▶ Fluoropyrimidine (fluorouracil<sup>a</sup> or capecitabine), oxaliplatin, and nivolumab for PD-L1 CPS ≥1 (category 1 for PD-L1 CPS ≥5)<sup>c,f,18</sup></li> <li>▶ Fluoropyrimidine (fluorouracil<sup>a</sup> or capecitabine), oxaliplatin, and pembrolizumab for PD-L1 CPS ≥1 (category 1 for PD-L1 CPS ≥5)<sup>c,f,19</sup></li> <li>▶ Fluoropyrimidine (fluorouracil<sup>a</sup> or capecitabine), oxaliplatin, and tislelizumab-jsgr for PD-L1 CPS ≥1 (category 1 for PD-L1 CPS ≥5)<sup>c,f,20</sup></li> <li>▶ Fluoropyrimidine (fluorouracil<sup>a</sup> or capecitabine), oxaliplatin, and zolbetuximab-clzb for CLDN18.2 positive<sup>b</sup> (category 1)<sup>21,22</sup></li> <li>▶ Fluoropyrimidine (fluorouracil<sup>a</sup> or capecitabine) and oxaliplatin<sup>23-25</sup></li> <li>▶ Fluoropyrimidine (fluorouracil<sup>a</sup> or capecitabine), cisplatin, and pembrolizumab for PD-L1 CPS ≥1 (category 1 for PD-L1 CPS ≥5)<sup>c,f,19</sup></li> <li>▶ Fluoropyrimidine (fluorouracil<sup>a</sup> or capecitabine), cisplatin, and tislelizumab-jsgr for PD-L1 CPS ≥1 (category 1 for PD-L1 CPS ≥5)<sup>c,f,20</sup></li> <li>▶ Fluoropyrimidine (fluorouracil<sup>a</sup> or capecitabine) and cisplatin<sup>23,26-28</sup></li> </ul> </li> <li>• MSI-H/dMMR tumors (independent of PD-L1 status)<sup>d</sup> <ul style="list-style-type: none"> <li>▶ Pembrolizumab<sup>c,f,29-31</sup></li> <li>▶ Dostarlimab-gxly<sup>c,f,32</sup></li> <li>▶ Nivolumab and ipilimumab<sup>c,f,18</sup></li> <li>▶ Fluoropyrimidine (fluorouracil<sup>a</sup> or capecitabine), oxaliplatin, and nivolumab<sup>c,f,18</sup></li> <li>▶ Fluoropyrimidine (fluorouracil<sup>a</sup> or capecitabine), oxaliplatin, and pembrolizumab<sup>c,f,30,31</sup></li> </ul> </li> </ul>
<p><b>Other Recommended Regimens</b></p> <ul style="list-style-type: none"> <li>• Fluorouracil<sup>a,g</sup> and irinotecan<sup>h,33</sup></li> <li>• Paclitaxel with or without carboplatin or cisplatin<sup>h,34-38</sup></li> <li>• Docetaxel with or without cisplatin<sup>h,39-42</sup></li> <li>• Fluoropyrimidine<sup>h,27,43,44</sup> (fluorouracil<sup>a</sup> or capecitabine)</li> <li>• Docetaxel, cisplatin or oxaliplatin, and fluorouracil<sup>a,h,45,46</sup></li> </ul>
<p><b>Useful in Certain Circumstances</b></p> <ul style="list-style-type: none"> <li>• Entrectinib, larotrectinib, or repotrectinib for <i>NTRK</i> gene fusion-positive tumors (category 2B)<sup>47-49</sup></li> </ul>

## Current indications for HER2-negative Gastric / GEJ cancer in the 1L setting

**Nivolumab  
(OPDIVO)**

**April 16, 2021**

- for adult patients with advanced or metastatic gastric cancer, GEJ cancer, and esophageal adenocarcinoma of whose tumors express **PD-L1 ( $\geq 1$ )** in combination with fluoropyrimidine- and platinum-containing chemotherapy

**Pembrolizumab  
(KEYTRUDA)**

**November 16, 2023**

- in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the **first-line treatment** of adults with locally advanced unresectable or metastatic **HER2-negative** gastric / GEJ adenocarcinoma whose tumors express **PD-L1 (CPS  $\geq 1$ )**

**Zolbetuximab  
(VYLOY)**

**October 18, 2024**

- a claudin 18.2-directed cytolytic antibody indicated in combination with fluoropyrimidine- and platinum-containing chemotherapy for the **first-line treatment** of adults with locally advanced unresectable or metastatic **HER2-negative** gastric or GEJ adenocarcinoma whose tumors are **claudin (CLDN) 18.2 positive**

**Tislelizumab  
(TEVIMBRA)**

**December 27, 2024**

- in combination with platinum and fluoropyrimidine-based chemotherapy in adults for the **first-line treatment** of unresectable or metastatic **HER2-negative** gastric or GEJ adenocarcinoma whose tumors express **PD-L1 ( $\geq 1$ )**

***How does PD-L1 impact your prescribing behavior based on indication?  
Do you experience any approval challenges if not used in the first line setting?***





# ARS Results from HCP Participants

**Will the challenging case discussed impact your prescribing behavior for patients with CLDN18.2 positive gastric/GEJ cancer in the 1L metastatic setting?**

**Yes, my prescribing behavior will change – more likely to test for and use a CLDN18.2 targeted treatment in the 1L setting**

63%

**No, my prescribing behavior will stay the same – preference for IO or trastuzumab-based regimen in the 1L setting**

33.30%

**Unsure**

3.70%

# ***Challenging Cases in Gastric/GEJ Cancer***

## **Gastric / GEJ Cancer**

*Patient Case: 1L metastatic untreated, inoperable*

- *Testing is critical*
  - *Turnaround times are challenging*
  - *Biomarker overlap may become a greater challenge*
- *Awareness of clinical trial data can impact treatment decisions*
- *Restrictive indications can limit treatment choices in later lines -> insurance issues*