

ORIGINAL ARTICLE

Temporal dynamics of CLDN18.2 expression following zolbetuximab treatment in advanced gastric cancer

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Background: Zolbetuximab plus chemotherapy is the standard of care for unresectable advanced gastric cancer that is human epidermal growth factor receptor 2-negative and claudin-18 isoform 2 (CLDN18.2)-positive (2+/3+ staining intensity in $\geq 75\%$ of tumor cells). The dynamics of CLDN18.2 expression after zolbetuximab remain poorly understood.

Materials and methods: Using immunohistochemistry, we retrospectively assessed CLDN18.2 expression in tumor samples from CLDN18.2-positive advanced gastric cancer collected before and after zolbetuximab-containing chemotherapy. Expression levels were evaluated based on the proportion of cells with $\geq 2+$ staining intensity using multiple cut-off values (75%, 40%, and 25%).

Results: Among 65 patients who received zolbetuximab-containing therapy, CLDN18.2 status was assessable at both baseline and disease progression in 15 patients. At disease progression, 53.3% of cases converted to CLDN18.2-negative. CLDN18.2 positivity was retained in 66.7% and 73.3% of patients when applying 40% and 25% cut-off levels, respectively.

Conclusions: CLDN18.2 expression above the $\geq 75\%$ cut-off declined after zolbetuximab, but lower-level expression was often preserved, supporting the potential for subsequent targeted therapy.

Key words: gastric cancer, CLDN18.2, zolbetuximab, biomarker, immunohistochemistry, targeted therapy

INTRODUCTION

Zolbetuximab is a chimeric monoclonal antibody that specifically targets claudin-18 isoform 2 (CLDN18.2), a tight junction protein highly expressed in gastric cancer (GC). Two global phase III trials (SPOTLIGHT and GLOW) independently demonstrated that zolbetuximab-containing chemotherapy significantly improved progression-free survival and overall survival in treatment-naïve patients with human epidermal growth factor receptor 2 (HER2)-negative and CLDN18.2-positive advanced GC or gastroesophageal junction cancer (GEJC), leading to its establishment as the standard first-line treatment for this patient population.¹⁻⁶ Currently, CLDN18.2-positive GC/GEJC is

defined as tumors with 2+ or 3+ staining intensity in $\geq 75\%$ of tumor cells, as applied in these studies.

After the success of zolbetuximab, multimodal approaches targeting CLDN18.2, including newer monoclonal antibodies, bispecific antibodies, antibody–drug conjugates, and chimeric antigen receptor T (CAR-T)-cell therapies, are now under investigation, mainly as second- or later-line therapies.^{7,8} Early-phase clinical trials of these novel CLDN18.2-directed therapies have demonstrated promising antitumor activity even with lower CLDN18.2 expression, suggesting a potential wider expansion of CLDN18.2-targeted therapy.^{7,8} However, data regarding the temporal dynamics of CLDN18.2 expression following first-line zolbetuximab-based therapy remain limited. This study examined temporal changes in CLDN18.2 expression after first-line zolbetuximab-containing therapy in patients with CLDN18.2-positive advanced GC/GEJC.

MATERIALS AND METHODS

Study design and patient selection

This observational study was conducted at the National Cancer Center Hospital East in Kashiwa, Japan. Eligible

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patients met the following criteria: histologically confirmed CLDN18.2-positive (2+ or 3+ staining intensity in $\geq 75\%$ of tumor cells) gastric or GEJ adenocarcinoma, unresectable advanced or recurrent disease, having received at least one cycle of first-line chemotherapy with zolbetuximab before 31 March 2025, primary tumor specimens from before and after treatment being available, and having provided written informed consent for treatment and biomarker analysis (UMIN000019129). Treatment dose and schedule were the same as those in the pivotal studies.^{1,2} This study was approved by the ethics committee of our institution, National Cancer Center Hospital East Certified Review Board (Approval ID: 2017-120, Approval date: 26 September 2017). All procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and its later versions.

Assessments

Clinicopathological characteristics were collected for each patient. CLDN18.2 expression was assessed in primary tumors using immunohistochemistry using CLDN18 antibody (Clone 43-14A, Roche Ventana). CLDN18.2 expression level was evaluated as weak (1+), moderate (2+), or strong expression (3+) staining intensity and CLDN18.2-positive tumor proportions were calculated. The proportion of positive tumor cells was assessed using cut-off values of 25%, 40%, and 75%, in accordance with criteria from clinical trials of CLDN18.2-targeted therapies.⁷ The timing and indication for biopsy after treatment were determined at the discretion of each physician.

Statistical analysis

Changes in CLDN18.2 expression levels from baseline to disease progression were visualized using Sankey diagrams based on two definitions of positivity: $\geq 2+$ and $\geq 1+$ staining intensity. All statistical analyses were carried out using R version 4.4.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient characteristics

A total of 65 consecutive patients received first-line zolbetuximab-containing chemotherapy; 29 experienced disease progression, and biopsy samples at progression were available in 20 patients. Tumor cells were not detected in 5 patients; CLDN18.2 expression status at disease progression was assessable in the remaining 15 patients.

The median age of patients with paired tumor samples from before treatment and at the time of disease progression was 68 years (range 37-82 years), and most had a gastric primary tumor (93.3%) and diffuse-type histology (86.7%). All patients were HER2-negative and were proficient in mismatch repair. Programmed death-ligand 1 expression, measured by combined positive score (CPS), was ≥ 1 in 93.0% of patients, including 33.3% with CPS ≥ 5 (Table 1).

Table 1. Characteristics of patients with paired tumor samples at baseline and at disease progression

Characteristics	n = 15	%
Age, years		
Median (Range)	68 (37-82)	—
Sex, n (%)		
Female	7	47
Male	8	53
ECOG PS, n (%)		
0	9	60
1	6	40
Primary site, n (%)		
Stomach	14	93
Gastroesophageal junction	1	7
Ascites, n (%)		
Present	8	53
Absent	7	47
Measurable lesion, n (%)		
Present	11	73
Absent	4	27
Metastatic lesions, n (%)		
Lymph node	11	73
Peritoneum	9	60
Liver	4	27
Histological type, n (%)		
Intestinal	2	13
Diffuse	13	87
Signet-ring cell component, n (%)		
Present	6	40
Absent	9	60
PD-L1 CPS, n (%)		
<1	1	7
1-4	9	60
≥ 5	5	33

CPS, combined positive score; ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1, programmed death-ligand 1.

Change of CLDN18.2 expression with zolbetuximab-containing therapy

Changes in CLDN18.2 expression from baseline to disease progression were visualized using Sankey diagrams (Figure 1A and B). CLDN18.2 expression with $\geq 2+$ intensity in $\geq 75\%$ of tumor cells was retained in 7/15 patients (46.7%). Using a cut-off of 40%, CLDN18.2 expression was maintained in 10 patients (66.7%), and in 11 patients when a 25% cut-off was applied (73.3%) (Figure 1A). CLDN18.2 expression with $\geq 1+$ intensity in $\geq 75\%$ of tumor cells was observed in 8/15 patients (53.3%). At both 40% and 25% cut-offs, expression was retained in 11 patients (73.3%) (Figure 1B). The median change in the proportion of CLDN18.2 tumor cells with $\geq 2+$ or $\geq 1+$ staining intensity from baseline to disease progression was -25% (range -100% to 20%) and -20% (range -97% to 20%), respectively.

Representative cases with dynamic change of CLDN18.2 expression during zolbetuximab therapy

In this article, we present two representative cases illustrating variations in CLDN18.2 expression during zolbetuximab-containing therapy. Case 1 was a 72-year-old woman who had GC with lymph node and peritoneal metastases. Baseline endoscopy revealed a circumferential type 4 tumor extending

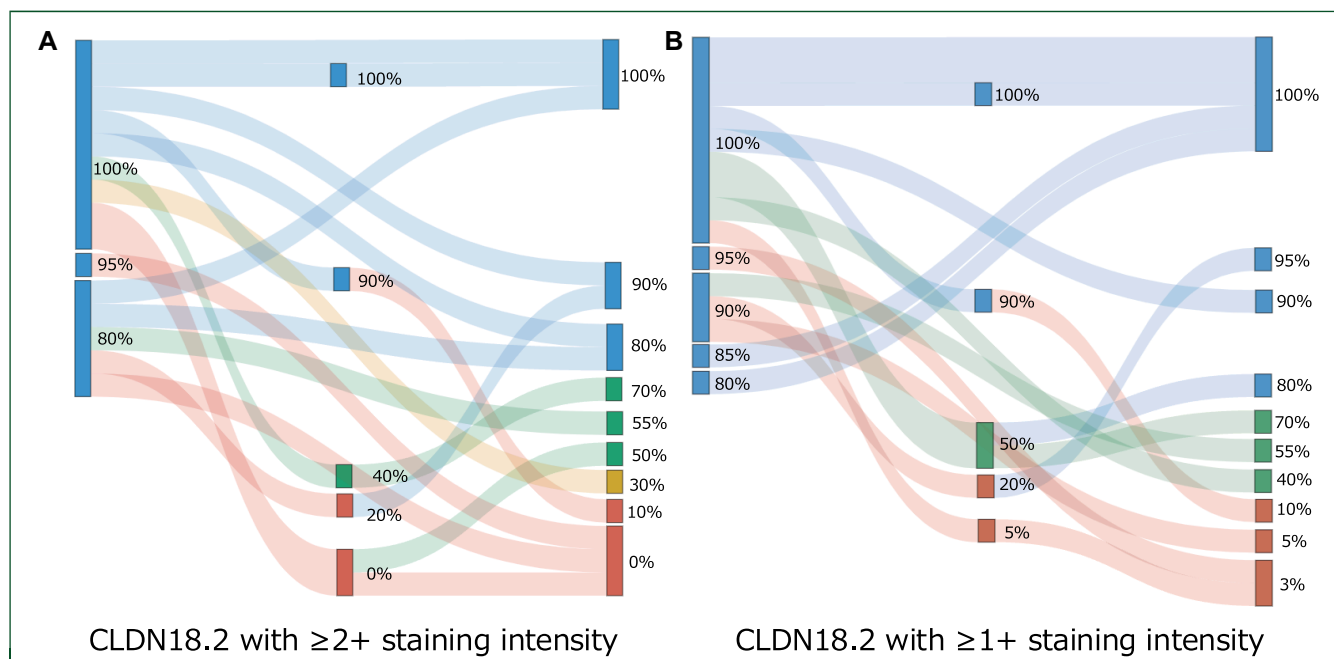


Figure 1. Changes in CLDN18.2 expression from baseline to disease progression with zolbetuximab. (A) CLDN18.2 with $\geq 2+$ staining intensity. (B) CLDN18.2 with $\geq 1+$ staining intensity. The Sankey diagram shows changes in the proportion of tumor cells with moderate-to-strong ($2+/3+$) CLDN18.2 staining intensity from baseline (left panel) to disease progression (right panel). Colors indicate different expression levels: blue for $\geq 75\%$, green for $\geq 40\%$ to $< 75\%$, brown for $\geq 25\%$ to $< 40\%$, and red for $< 25\%$. The width of each flow represents the proportion of patients showing the corresponding change in expression levels. Values indicate the percentage of CLDN18.2-positive tumor cells.

from the upper gastric body to the pyloric region, and biopsy confirmed poorly differentiated adenocarcinoma with a signet-ring cell component with CLDN18.2-positive expression ($3+$ in 90% of tumor cells; $2+$ in 10%). During treatment, endoscopy carried out 9 months after treatment initiation showed no apparent changes in the primary lesion, though CLDN18.2 expression was reduced ($3+$ in 10%, $2+$ in 30%, $1+$ in 10%, and 0 in 50%). At 12 months, endoscopy at disease progression revealed that the primary tumor had expanded more extensively compared with baseline. At that time, CLDN18.2 expression was restored, with $3+$ intensity in 50%, $2+$ in 20%, and $1+$ in 10% of tumor cells (Figure 2A).

The second case was a 76-year-old man with advanced diffuse-type adenocarcinoma of the GEJ with liver metastases and pleural dissemination. CLDN18.2 expression at baseline was $3+$ in 95% and $2+$ in 5% of tumor cells. Endoscopy carried out 5 months after treatment initiation showed no apparent change in the primary lesion, and CLDN18.2 expression was largely maintained ($3+$ in 80%, $2+$ in 10%). At 7 months, endoscopy at disease progression revealed that CLDN18.2 expression was markedly decreased, with $3+$ intensity observed in 5% and $2+$ in 5% of tumor cells (Figure 2B).

These two cases illustrate the dynamic change of CLDN18.2 expression during zolbetuximab therapy. Although case 1 exhibited a transient decrease followed by partial restoration at disease progression, case 2 showed sustained CLDN18.2 expression before a sharp decline at disease progression. In both cases, temporal changes in CLDN18.2 expression were not associated with response to zolbetuximab-containing

therapy. Further investigations are warranted to elucidate the clinical significance of CLDN18.2 dynamics.

DISCUSSION

To the best of our knowledge, this is the first report demonstrating temporal changes in CLDN18.2 expression from baseline to disease progression in patients treated with zolbetuximab-containing chemotherapy. CLDN18.2 positivity ($\geq 2+$ in $\geq 75\%$ of tumor cells) was maintained in 46.7% of patients at the disease progression to zolbetuximab-containing therapy. Previous studies have also reported reduced CLDN 18.2 expression in 40%-60% of patients after chemotherapies without CLDN18.2-targeted agents, although their sample sizes were relatively small.⁹⁻¹¹ Intratumoral heterogeneity is also a major limitation when evaluating small biopsy samples. Recent studies have reported heterogeneous expression of CLDN18.2 in primary lesion.¹² Further investigation is warranted to determine whether CLDN18.2 expression is more likely to decrease following CLDN18.2-targeted therapy.

The expression of CLDN18 is regulated by transactivation through T/EBP/NKX2.1 (TTF-1); however, methylation of the CLDN18 promoter region can inhibit TTF-1 binding, reducing the expression of CLDN18.^{13,14} In general, chemotherapy-induced cytotoxic stress can lead to DNA methylation, which may be an underlying mechanism for the decreased expression of CLDN18.2 during cytotoxic chemotherapy. A preclinical study indicated that the relevance of the transcription factor

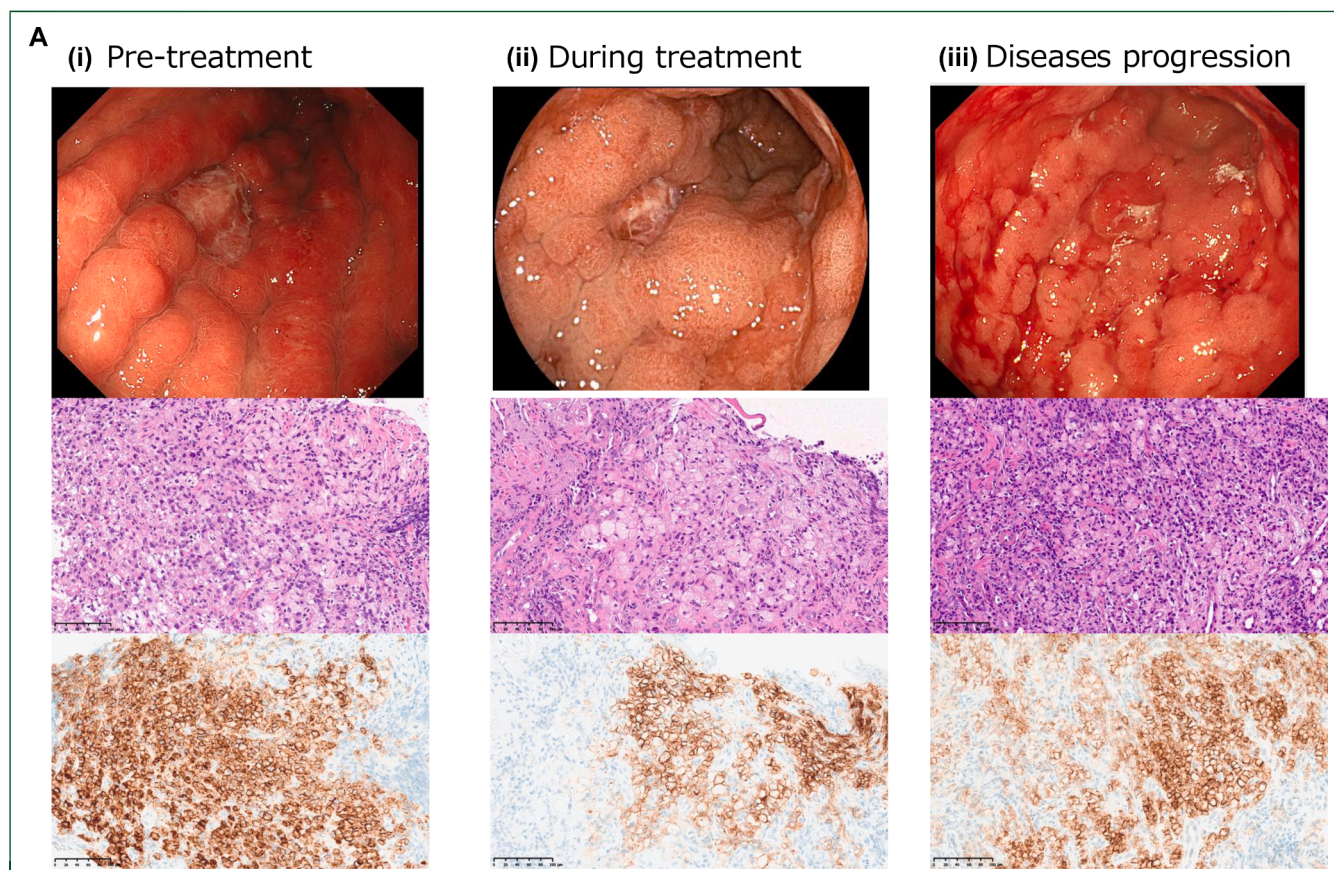


Figure 2. Representative cases with CLDN18.2 expression of $\geq 2+$ staining intensity, showing changes during zolbetuximab treatment. CLDN18.2 expression was evaluated using immunohistochemistry (CLDN18 antibody, Clone 43-14A, Ventana) and categorized based on staining intensity (0, 1+, 2+, 3+). Endoscopic images (top), H&E staining (middle), and CLDN18.2 immunohistochemistry (bottom) of primary tumors at three time points: pre-treatment, during treatment, and at disease progression. (A) Case 1: a 72-year-old woman with type 4 advanced gastric cancer. CLDN18.2 expression was high at baseline (3+: 90%, 2+: 10%), decreased during treatment (3+: 10%, 2+: 30%, 1+: 10%), followed by partial recovery at disease progression (3+: 50%, 2+: 20%, 1+: 10%). (B) Case 2: a 76-year-old man with type 3 advanced gastroesophageal junction cancer. CLDN18.2 expression was high at baseline (3+: 95%, 2+: 5%), remained high during treatment (3+: 80%, 2+: 10%), but sharply decreased at progression (3+: 5%, 2+: 5%). Scale bars in histological images represent 100 μ m.

was limited, suggesting that another mechanism may regulate CLDN18.2 expression.¹⁴ Previous studies have demonstrated decreased CLDN18.2 expression in metastatic sites such as the liver and peritoneum compared with primary tumors.^{15,16} Additionally, CLDN18.2 expression has been shown to decline from the superficial area toward the invasive front.¹⁵ These findings suggest that epithelial–mesenchymal transition may contribute to the reduction of expression of CLDN18.2, which may be a plastic and reversible process.

In the context of reduction of expression of the target protein as a result of clonal selection during targeted therapy, decreased CLDN18.2 expression may represent a resistance mechanism, similar to HER2 loss during anti-HER2 therapy.^{17–20} However, considering its reversibility, the reduction of expression of CLDN18.2 may be transient with different biological implications compared with target molecules involved in signal transduction such as HER2.

Using lower cut-off values of 40% and 25%, 66.7% and 73.3% of cases retained tumors expressing CLDN18.2 with $\geq 2+$ staining intensity, respectively. When any CLDN18.2 expression

($\geq 1+$) was considered, CLDN18.2 positivity was preserved in 73.3% of cases at both cut-off levels. These results suggest that patients previously treated with chemotherapy and zolbetuximab may still be eligible for novel CLDN18.2-targeted therapies in subsequent lines of treatment. Emerging CLDN18.2-targeted therapies, including antibody–drug conjugates,^{21,22} bispecific antibodies,²³ and CAR-T cells,²⁴ have demonstrated promising antitumor activity in clinical trials that adopted lower cut-offs for CLDN18.2 positivity.

Our study had several limitations. Selection bias may exist, as only patients with assessable paired pre- and post-treatment samples were included. Additionally, CLDN18.2 expression was assessed using limited biopsy samples, which may not fully capture intratumoral heterogeneity. This study included only a single arm of zolbetuximab-containing therapy without a chemotherapy-alone comparator. Therefore, it remains unclear whether the reduced expression was attributable to the chemotherapy components, zolbetuximab, or both. These limitations should be considered when interpreting the findings.

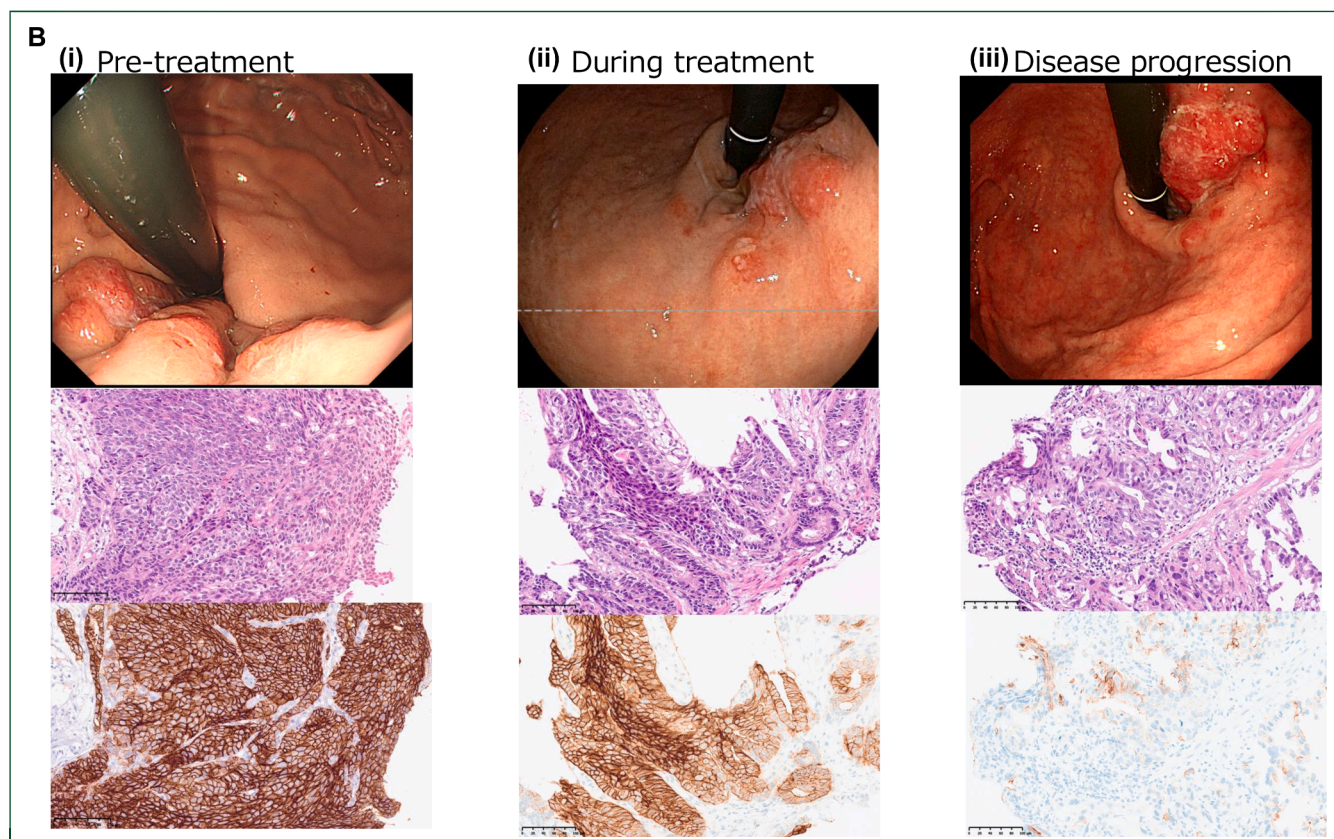


Figure 2. Continued.

Conclusions

CLDN18.2 positivity ($\geq 2+$ in $\geq 75\%$ of tumor cells) in GC/GEJC was maintained at disease progression in 46.7% of patients treated with zolbetuximab-containing therapy. When lower cut-offs (40% and 25%) were applied, positivity rates increased to 66.7% and 73.3%, respectively. These findings suggest that patients initially classified as CLDN18.2-positive may remain eligible for subsequent CLDN18.2-targeted therapies. Further studies are required to validate these observations and to elucidate the potential role of CLDN18.2 dynamics as a predictive biomarker for later-line CLDN18.2-directed treatment.

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DATA SHARING

The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

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