# Successful treatment with trastuzumab plus chemotherapy as the first-line regimen in advanced small bowel adenocarcinoma harboring HER2 amplification: A report of two cases

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**Abstract.** Therapeutic options are limited for individuals with unresectable or metastatic small bowel adenocarcinoma (SBA), necessitating palliative chemotherapy. Human epidermal growth factor receptor 2 (HER2) gene amplification or protein overexpression in SBA is exceedingly rare. HER2 amplification mutations/overexpression serves as a potential target for treatment in various malignancies. However, research on targeted therapies for SBA with *HER2* mutation is lacking. In this context, the present study reports two cases of advanced SBA with a *HER2* amplification mutation. Both patients received the anti-HER2 agent trastuzumab in combination with an oxaliplatin-based chemotherapy regimen as a first-line treatment. Following disease progression, trastuzumab was used in conjunction with other palliative chemotherapy regimens. Notably, anti-HER2 treatment resulted in significantly extended overall survival times without the occurrence of serious treatment-related adverse events. The overall survival times of the two patients were 31 and 15 months. Additionally, a review of the existing literature was conducted with regard to the effectiveness of anti-HER2 agents in the treatment of advanced SBA. It can be concluded that it is imperative to ascertain the HER2 status prior to the initiation of palliative treatment.

## Introduction

Small bowel adenocarcinoma (SBA) is a rare disease, constituting ~2% of gastrointestinal malignancies and 30% of all small intestinal malignancies (1,2). Owing to its inconspicuous location and aggressive biological behavior, patients with SBA are often diagnosed at an advanced stage, resulting in a prognosis less favorable than that of patients with colorectal cancer (3). Therapeutic options are limited for individuals with unresectable or metastatic SBA. In comparison to best supportive care, palliative chemotherapy with a fluoropyrimidine-based regimen has been shown to extend the median overall survival (OS) time by ~10 months (4). However, due to its rarity, prospective research into targeted therapies for the treatment of SBA is lacking. A recent prospective analysis of clinical samples from patients with SBA revealed *HER2* amplification mutations in 2.2% of cases (5). Over the past 20 years, HER2-targeted therapies have significantly improved the prognosis of breast, gastric and colorectal cancer in cases of HER2 overexpression and/or amplification (6). Data from the ToGA trial demonstrated that, when used in patients with chemotherapy-naive HER2-positive advanced gastric cancer, chemotherapy plus trastuzumab (an anti-HER2 monoclonal antibody) significantly increased the overall response rate (ORR) by 12.8% and extended the median OS time by 2.7 months when compared to chemotherapy alone (7). In the HERACLES trial, patients with HER2-positive metastatic colorectal cancer refractory to standard care received dual-targeted therapy with trastuzumab and lapatinib. The results indicated that the combination therapy was effective, with an objective response rate of 30%, and was well tolerated (8). Considering the successful application of anti-HER2 agents in these digestive system malignancies, it is suggested that patients with SBA harboring HER2 amplification/overexpression may benefit from the administration of an anti-HER2 monoclonal antibody. The present study describes two cases of advanced SBA that harbored *HER2* amplification mutations and in which the patients achieved prolonged survival times from frontline treatment with anti-HER2 therapy in combination with chemotherapy.

## Case report

*Case one*. A 75-year-old man presented to Huadong Hospital Affiliated to Fudan University (Shanghai, China) in August 2019 with swelling and pain in the left leg that had persisted for 1 month. A computed tomography (CT) scan revealed enlarged lymph nodes in the abdominal cavity and retroperitoneum. Subsequent positron emission tomography-CT (PET-CT) identified multiple enlarged lymph nodes in the abdominal cavity and a lesion on the abdominal wall exhibiting increased 18F-fluorodeoxyglucose (18F-FDG) metabolism. Gastroscopy

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indicated mucosal roughness in the duodenal papillary region. For histological diagnosis, a tissue biopsy was performed. Sections with a thickness of 4 $\mu$m were made from formalin-fixed paraffin-embedded (FFPE) tissues. Hematoxylin-and-eosin (H&E)-staining was performed using the Dako Coverstainer (Dako; Agilent Technologies, Inc.) according to the manufacturer's instructions. Immunohistochemistry was performed using the Lumatas Autostaining System, as instructed by the manufacturer (Lumatas Biosystems). The primary antibodies used were as follows: Cytokeratin 7 (CK7; 1:100; rat; cat. no. MAB-0828; clone MX053; Fuzhou Maixin Biotech Co., Ltd.), CK20 (1:100; rat; cat. no. MAB-0834; clone MX059; Fuzhou Maixin Biotech Co., Ltd.), caudal type homeobox transcription factor 2 (CDX2; undiluted; rabbit; cat. no. RMA-0631; clone EPR2764Y; Fuzhou Maixin Biotech Co., Ltd.), HER2 (rabbit; undiluted; cat. no. Kit-0043; clone MXR001; Fuzhou Maixin Biotech Co., Ltd.). The pathologist used an inverted microscope to examine all slides. The lesion was confirmed as an adenocarcinoma, with the following expression: CK7(+) (data not shown), CK20(+),CDX-2(+) and HER2(++) (Fig. 1). The pathological diagnosis of the abdominal wall lesion was metastatic adenocarcinoma with the following immunohistochemical expression: CK(+) (data not shown) and HER2(++) (Fig. 2). Furthermore, fluorescence *in situ* hybridization (FISH) was carried out using the *HER2* kit (Zyto Light FISH-Tissue Implementation Kit; cat. no. Z-2028-5; ZytoLight CEN 17/SPEC ERBB2 Dual Colour Probe; cat. no. Z-2077-50; ZytoVision GmbH) on 4-$\mu$m FFPE tissue sections, according to the manufacturer's instructions. *HER2* amplification was revealed in both the duodenal tumor [*HER2*/*CEP17* (chromosome 17 enumeration probe) ratio, 3.32; *HER2* copy number, 9.07 copies/cell] (Fig. 1) and the abdominal wall lesion (*HER2*/*CEP17* ratio, >2.0; *HER2* copy number, >6.0 copies/cell) (Fig. 2). Consequently, the diagnosis of advanced SBA harboring *HER2* amplification was confirmed.

Given the infeasibility of radical surgery, the patient commenced trastuzumab treatment (8 mg/kg loading dose, then 6 mg/kg on day 1, intravenously) in combination with capecitabine (1,000 mg/m$^2$ twice daily on days 2-15, orally) and oxaliplatin (130 mg/m$^2$ on day 2, intravenously) every 3 weeks for 10 cycles from September 2019. According to the Response Criteria Evaluation in Solid Tumors version 1.1 (9), the sum of the longest diameters of the target lesions decreased by >30%, as shown by CT scan, thus a partial response (PR) was achieved after three cycles (Fig. 3). From April 2020 to January 2021, the patient received sequential maintenance therapy with trastuzumab (6 mg/kg on day 1, intravenously) and capecitabine (1,000 mg/m$^2$ twice daily on days 1-14, orally) every 3 weeks for 13 cycles. Unfortunately, progressive disease (PD) occurred in February 2021, resulting in a progression-free survival (PFS) time of 15 months for the first-line treatment. Subsequently, trastuzumab (4 mg/kg on day 1, intravenously) in combination with modified FOLFOX (comprising 5-fluorouracil as an intravenous bolus of 400 mg/m$^2$ and then a continuous 46-h infusion of 2,400 mg/m$^2$ on day 2, intravenous leucovorin at 400 mg/m$^2$ on day 2 and intravenous oxaliplatin at 85 mg/m$^2$ on day 2) was administered every 2 weeks as the second-line regimen for nine cycles, providing a PR. To mitigate neurotoxicity (Common Terminology Criteria for Adverse Events grade 3) (10), trastuzumab (4 mg/kg on day 1, intravenously) was subsequently combined with 5-fluorouracil (intravenous bolus of 400 mg/m$^2$ and then a continuous 46-h infusion of 2,400 mg/m$^2$ on day 2) and leucovorin (400 mg/m$^2$ on day 2, intravenously) as maintenance therapy every 2 weeks. The second PD state occurred in January 2022, with a PFS time of 11 months for the second-line treatment. The patient was then treated with FOLFIRI (comprising 5-fluorouracil as an intravenous bolus of 400 mg/m$^2$ and then a continuous 46-h infusion of 2,400 mg/m$^2$ on day 1, intravenous leucovorin at 400 mg/m$^2$ on day 1 and intravenous irinotecan at 180 mg/m$^2$ on day 1, every 2 weeks) as the third-line therapy. The patient died following the development of pleural metastasis and massive pleural effusion in April 2022, with an OS time of 31 months.

*Case two*. A 28-year-old man presented to Huadong Hospital Affiliated to Fudan University with a 10-month history of intermittent vomiting, melena and upper abdominal pain, leading to hospitalization in November 2020. PET-CT revealed a malignant small intestinal tumor (maximum diameter, 31 mm) exhibiting increased 18F-FDG uptake. Multiple metastases were identified in the liver, bilateral lungs and pelvic cavity. The patient subsequently underwent a liver biopsy. Sections with a thickness of 4 $\mu$m were made from FFPE tissues. H&E-staining and immunohistochemistry were performed as aforementioned. The primary antibodies CK7, CK20, CDX2 and HER2 were used as aforementioned. Additional antibodies included the following: CK19 (1:100; rat; cat. no. MAB-0829; clone MX054; Fuzhou Maixin Biotech Co., Ltd.), carbohydrate antigen 19-9 (CA19-9; undiluted; rat; cat. no. MAB-0778; clone 121SLE; Fuzhou Maixin Biotech Co., Ltd.), carcinoembryonic antigen (CEA; undiluted; rat; cat. no. MAB-0852; clone MX068; Fuzhou Maixin Biotech Co., Ltd.) and $\alpha$1-fetoprotein (AFP; undiluted; rabbit; cat. no. RMA-1069; clone EP209; Fuzhou Maixin Biotech Co., Ltd.). Histopathological examination revealed intrahepatic metastatic adenocarcinoma, and immunohistochemical examinations showed the following results: CK7(+) (data not shown), CK19(+) (data not shown), CK20 (+), CDX-2(+),CA19-9(+) (data not shown), CEA(+) (data not shown), HER-2(+++) and AFP(-) (data not shown) (Fig. 4). Furthermore, *HER2* amplification was confirmed by FISH testing (*HER2*/*CEP17* ratio, >2.0, test method and regents were as described previously) (Fig. 4). Based on the pathological evaluation of tissue samples from the liver biopsy and the imaging diagnosis of a malignant mass in the small intestine, the patient was diagnosed with stage IV (AJCC, 8th edition) (11) SBA. Treatment with trastuzumab (6 mg/kg loading dose, then 4 mg/kg on day 1, intravenously) in combination with modified FOLFOX (comprising 5-fluorouracil as an intravenous bolus of 400 mg/m$^2$ and then a continuous 46-h infusion of 2,400 mg/m$^2$ on day 2, intravenous leucovorin at 400 mg/m$^2$ on day 2 and intravenous oxaliplatin at 85 mg/m$^2$ on day 2) every 2 weeks for eight cycles commenced in December 2020. A PR was evident after four cycles, resulting in a PFS time of 8 months (Fig. 5). Upon disease progression, the patient underwent second-line treatment, receiving trastuzumab (4 mg/kg on day 1, intravenously) in combination with FOLFIRI (comprising 5-fluorouracil as an intravenous bolus of 400 mg/m$^2$ and then a continuous 46-h infusion of 2,400 mg/m$^2$ on day 2, intravenous leucovorin at 400 mg/m$^2$ on day 2 and intravenous irinotecan at 180 mg/m$^2$

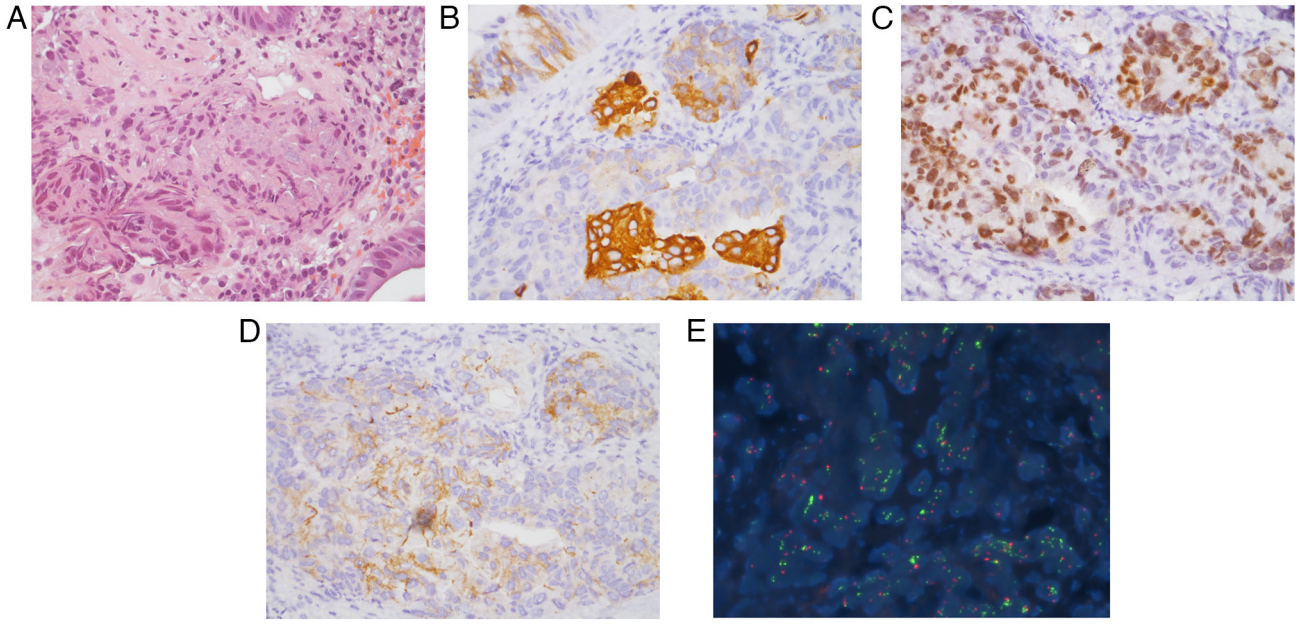


Figure 1. Histopathological and immunohistochemical features of small bowel adenocarcinoma (magnification, x400). (A) Histopathological examination of duodenal lesion biopsies using hematoxylin and eosin staining revealing duodenal adenocarcinoma. (B) Tumor cells displaying cytokeratin 20 expression. (C) Tumor cells showing homeobox protein CDX-2 expression. (D) Tumor cells exhibiting moderately stained membranous HER2 positivity (++). (E) FISH detection confirming HER2 gene amplification. Green signals indicate the HER2 probe and red signals indicate the CEP17 probe.

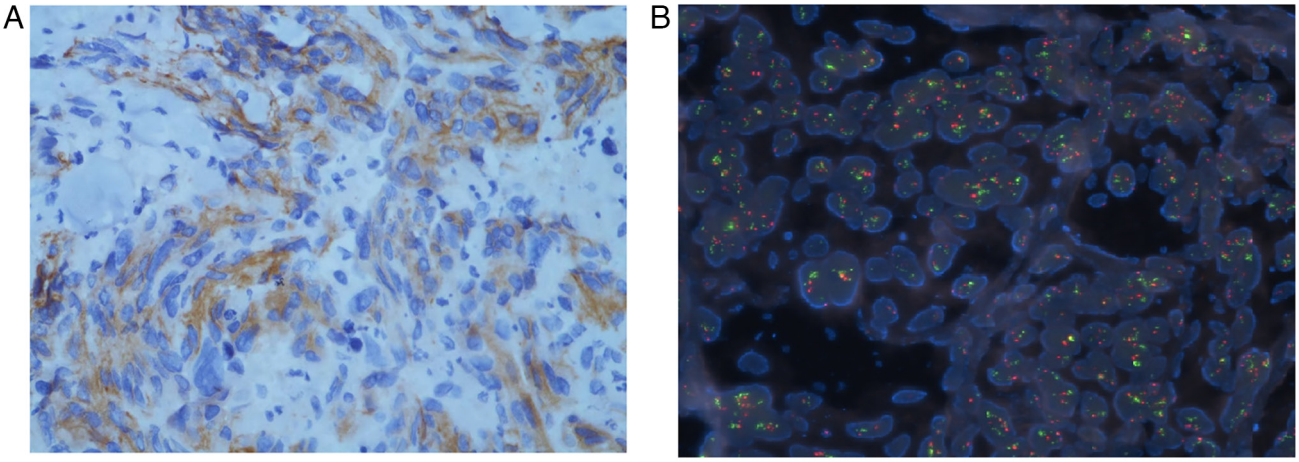


Figure 2. Histopathological and immunohistochemical characteristics of the abdominal wall lesion showing alignment with those of small bowel adenocarcinoma (magnification, x400). (A) Tumor cells demonstrating moderately stained membranous HER2 positivity (++). (B) Fluorescence *in situ* hybridization detection indicating HER2 gene amplification positivity in the tumor cells.

on day 2) every 2 weeks for four cycles starting in August 2021. The treatment course was interrupted several times due to intestinal obstruction and sinus bradycardia. The patient experienced further disease progression in December 2021. Best supportive care was provided and the patient succumbed to the disease in March 2022, with an OS time of 15 months.

## Discussion

The protein HER2, a transmembrane protein with tyrosine protein kinase activity, belongs to the epidermal growth factor receptor (EGFR) family. HER2, through homodimerization or heterodimerization with other family members, such as HER3, activates its intracellular tyrosine kinase domain. This, in turn, triggers downstream pathway activation, regulating cell proliferation and differentiation (12). HER2 positivity, which includes overexpression and amplification, is associated with aggressive tumor behavior and poor survival, and has been observed in various tumor types, including breast, lung, gastric and colorectal cancer (6). Trastuzumab, a monoclonal antibody targeting the extracellular domain of HER2, has proven effective in reducing recurrence and extending survival in these cancer types (7,13).

In the context of intestinal malignancies, HER2 research has primarily focused on patients with colorectal cancer (CRC). Approximately 3% of patients with metastatic CRC (mCRC) have been reported as HER2-positive (14). While a previous retrospective study showed no significant correlation between

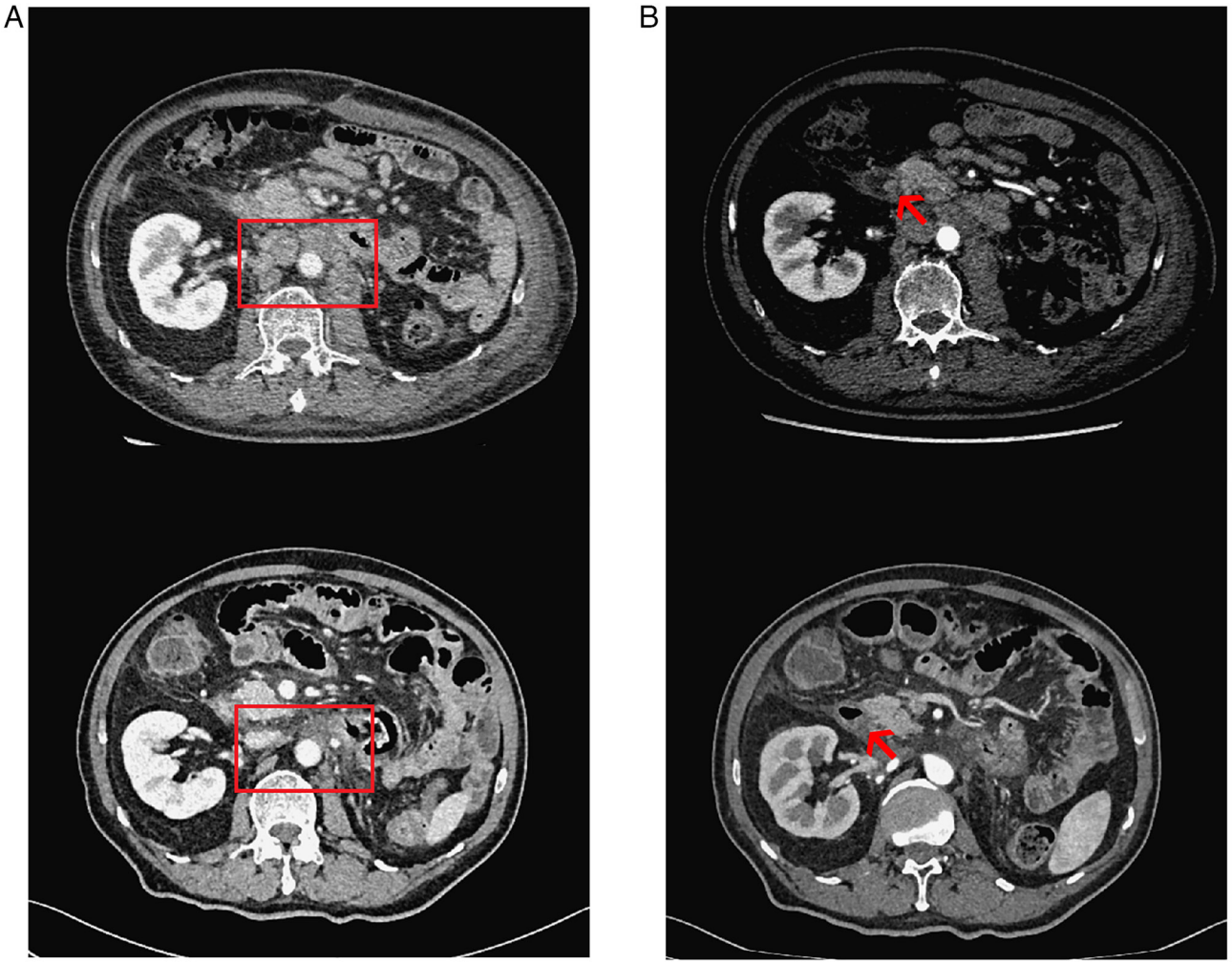


Figure 3. Contrast-enhanced CT scans of case one. (A) Abdominal CT images revealing multiple enlarged lymph nodes in the abdominal cavity and retroperitoneum at the initial assessment (August 2019) and a reduction in size after treatment (April 2020). (B) Abdominal CT images revealing a marked reduction in the size of the initial duodenal lesion (August 2019) following treatment (April 2020). CT, computed tomography.

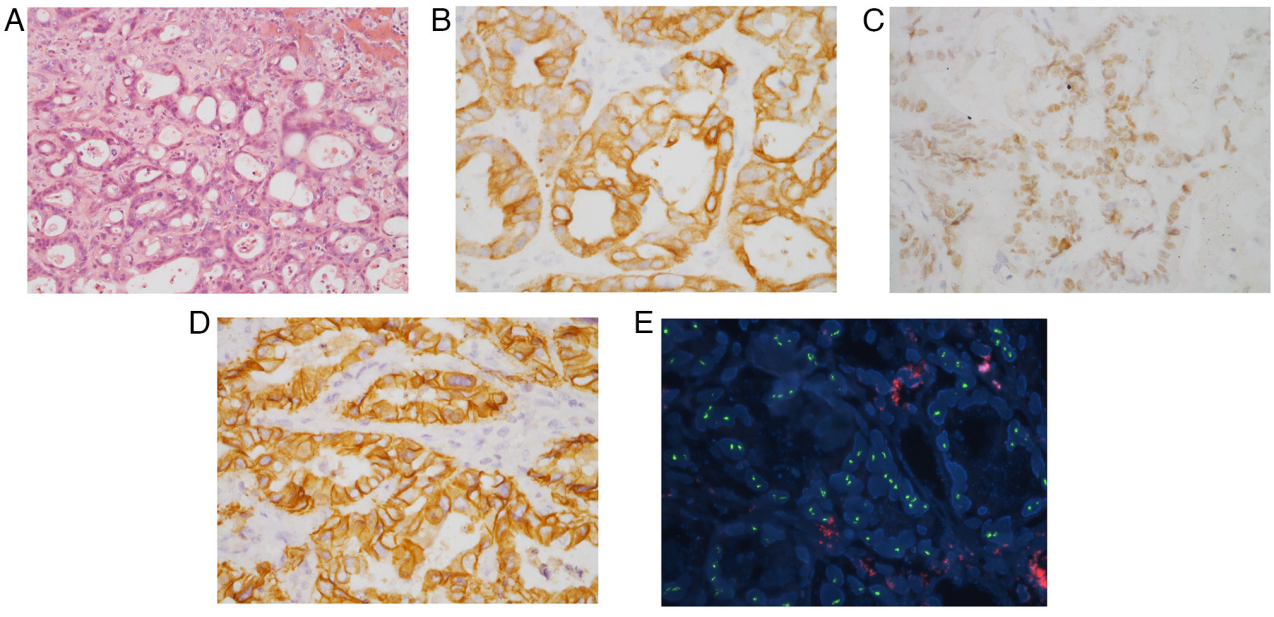


Figure 4. Histopathological and immunohistochemical characteristics of the intrahepatic metastatic lesion (magnification, x400). (A) Biopsied tissues stained with hematoxylin and eosin revealing adenocarcinoma cell infiltration. (B) Positive staining for cytokeratin 20 in tumor cells. (C) Positive staining for homeobox protein CDX-2 in tumor cells. (D) Strongly positive staining for HER2 (+++). (E) FISH detection demonstrating HER2 gene amplification. Green signals indicate the HER2 probe and red signals indicate the CEP17 probe.

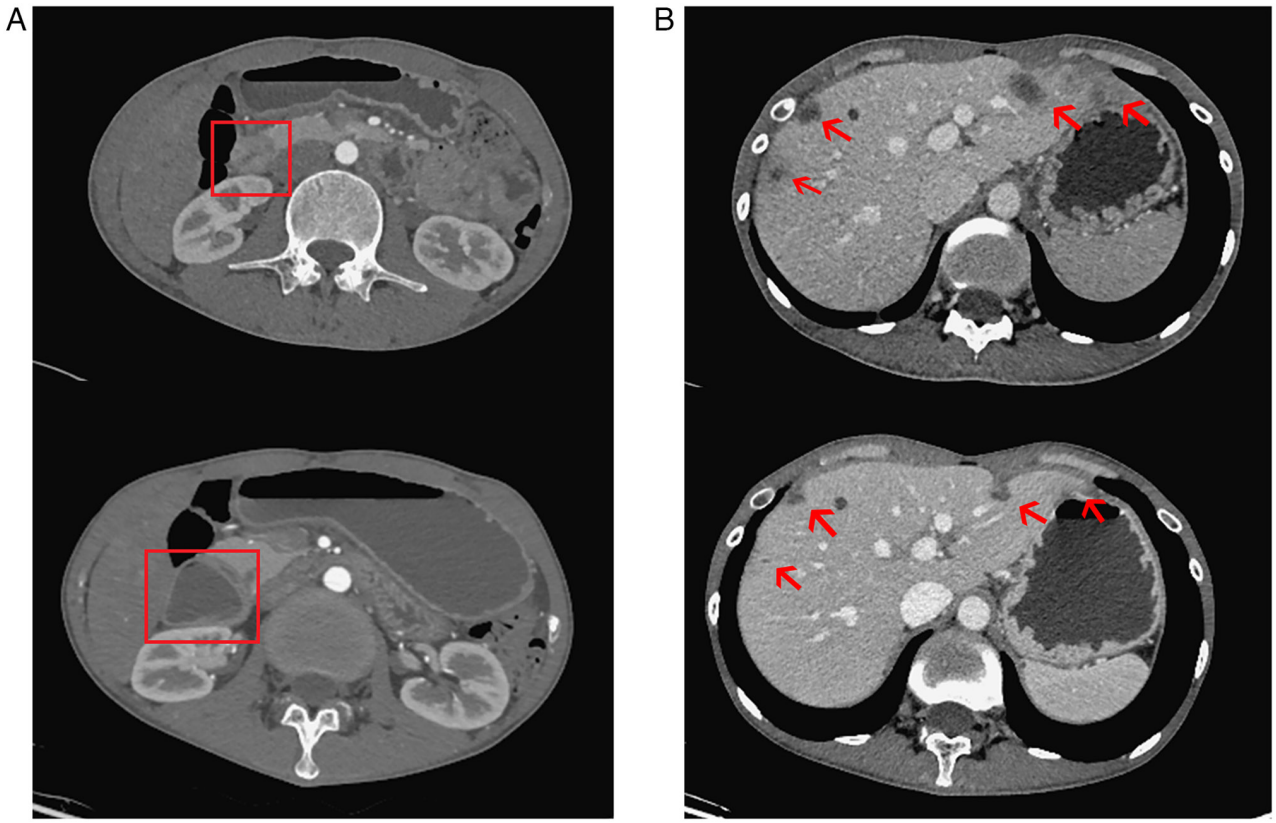


Figure 5. Contrast-enhanced CT scans of case two. (A) Abdominal CT images illustrating the duodenal mass causing bowel wall thickening and intestinal stenosis (November 2020), which was significantly alleviated after four cycles of trastuzumab in combination with 5-fluorouracil, leucovorin and oxaliplatin (March 2021). (B) Abdominal CT images revealing multiple intrahepatic metastatic lesions (November 2020) that diminished in size after treatment (March 2021). CT, computed tomography.

HER2 positivity and prognosis in CRC across all disease stages (15), more recent research data have confirmed that HER2 positivity is not only an independent risk factor for the OS of patients with stage III and IV colorectal cancer, but can also predict unresponsiveness to anti-EGFR therapy (16,17). It has been reported that anti-HER2 agents can achieve an ~30% ORR in pretreated patients with *HER2*-amplified mCRC (8,16). In addition to their effectiveness, these regimens have demonstrated good tolerability. The most commonly reported treatment-emergent adverse events (TRAEs) in dual HER2-targeted therapy or anti-HER2 antibody therapy in combination with chemotherapy are diarrhea, nausea and abdominal pain, among others. More severe TRAEs such as perforation, gastrointestinal bleeding and obstruction have not been observed, and no treatment-related deaths have been reported (8,18,19). While some researchers have suggested that the application of trastuzumab at different stages of mCRC treatment has no impact on survival, a tendency toward improved prognosis has been noted when it is used in the first line of treatment (14).

While immunotherapy has achieved considerable success in other advanced cancer types, including lung, gastric and oesophageal cancer, programmed cell death protein 1 (PD-1) immune checkpoint inhibition has not significantly improved the prognosis of advanced SBA. In the ZEBRA clinical trial, pretreated patients with advanced SBA, irrespective of their microsatellite instability/mismatch repair status, were administered pembrolizumab. The results revealed an ORR of only 8%, which did not meet the predefined success criteria of a 30% ORR (20). Given the absence of effective later-line treatment regimens, potentially targetable genomic alterations have been explored in SBA. A recent study by Pan *et al* (21) found that 30.3% of patients with SBA had various *HER2* genetic alterations, including amplifications. These alterations were demonstrated to be unrelated to recurrence-free survival. Laforest *et al* (22) observed two types of *HER2* alterations in 10% of patients with SBA. Among these, *HER2* amplification accounted for only 3.6%, while the remainder consisted of *HER2* mutations. All the *HER2* amplification cases were located in the ileum. No significant correlations were found between tumor stage or grade and *HER2* alterations. Due to the extremely low incidence of HER2-positive SBA, the clinical features, the predictive impact of HER2 positivity and the effectiveness of anti-HER2 agents in this population remain uncertain.

Case reports focusing on this rare disease are scarce. Hamad *et al* (23) reported the use of neoadjuvant treatment with the trastuzumab and FOLFOX regimen in a *HER2*-amplified duodenal cancer. After four cycles, the patient underwent radical surgery and achieved a complete pathological response. It was considered that the added benefit of trastuzumab resulted in a favorable surgical outcome. Wang *et al* (24) documented a case treated with oxaliplatin and capecitabine as first-line therapy and with a PD-1 inhibitor as second-line treatment. Maintenance therapy containing trastuzumab was administered, and the patient

achieved an OS time of >10 months (25). Consistent with these cases, the patients in the present study received trastuzumab in combination with oxaliplatin-based chemotherapy as the first-line regimen and achieved a PR. In the first case, the PFS time for the first-line therapy reached 17 months, and the OS exceeded 31 months. Trastuzumab was subsequently applied in both cases, with one patient experiencing a noticeable survival benefit.

According to previous research regarding chemotherapy in unresectable or metastatic SBA, the median PFS time for first-line therapy ranges from 5 to 11.3 months, and the median OS time ranges from 8 to 20.4 months (25). Therefore, we posit that the inclusion of trastuzumab in the first-line therapy contributed to the extension of survival in the two patients in the present study.

In conclusion, the present cases illustrate that the combination of trastuzumab and oxaliplatin-based chemotherapy as a first-line regimen has the potential to enhance the prognosis of patients with HER2-positive SBA. It is imperative to ascertain the HER2 status of a patient before commencing palliative treatment.

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**Availability of data and materials**

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

**Authors' contributions**

JW and XT were responsible for study conception and design. XT supervised the study. Data acquisition and formal analysis was performed by XZ, JC and FL. JW drafted the article. All authors read and approved the final manuscript. JW and XT confirm the authenticity of all the raw data.

**Ethics approval and consent to participate**

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Ethical approval was waived by the Medical Ethics Committee of Huadong Hospital Affiliated to Fudan University for the publication of this case report.

**Patient consent for publication**

Informed consent was obtained from the family member of each patient for the publication of this case report, including medical data and images.

**Competing interests**

The authors declare that they have no competing interests.

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