Case Report

Successful outcome of neoadjuvant PD-1 blockade, VEGFR-2 inhibitor plus chemotherapy for potentially unresectable esophagogastric junctional squamous cell carcinoma: a case report

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Background: Esophagogastric junctional squamous cell carcinoma (EJSCC) is quite rare among all gastric carcinoma, its potential resectable rate is low due to the late diagnosis. Recently, programmed death-1 (PD-1) blockade combined with anti-angiogenesis have gained accumulated clinical experiences in treating solid tumors. This is the first reported case with EJSCC who achieved a partial remission (PR) after neoadjuvant PD-1 blockade, vascular endothelial growth factor receptor 2 (VEGFR-2) inhibitor plus chemotherapy.

Case Description: We present an EJSCC case treated with novel neoadjuvant treatment. A 64-year-old Chinese male had the symptom of chocking for 3 months. An enhanced abdominal computed tomography (CT) scan found a locally advanced, potentially unresectable esophagogastric junctional (EGJ) mass, and the preoperative immunohistochemistry result exhibited a highly positive programmed death-ligand 1 (PD-L1) expression, so the patient received three courses of neoadjuvant camrelizumab (200 mg/day), apatinib (750 mg/day), albumin paclitaxel (200 mg/day) and nedaplatin (70 mg/day), he was well tolerant without any adverse event, and he underwent radical surgery after a significant tumor shrinkage. The patient recovered well after surgery, and he has received four cycles of camrelizumab and apatinib as maintenance treatment. There is no recurrence 7 months after surgery.

Conclusions: PD-1 blockade, VEGFR-2 inhibitor plus chemotherapy is effective and safe for the patient with EJSCC.

Keywords: Programmed death-1 blockade (PD-1 blockade); vascular endothelial growth factor receptor 2 inhibitor (VEGFR-2 inhibitor); esophagogastric junction; squamous cell carcinoma (SCC); case report

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Introduction

Gastric squamous cell carcinoma (SCC) is a rare malignancy, its incidence is less than 2% among all gastric cancers, and esophagogastric junctional SCC (EJSCC) occupies over 80% (1). The hypothesis of gastric SCC origin has been proposed that it arises from the squamous metaplastic epithelium or heterotopic squamous epithelium (2). Epstein-Barr virus (EBV) infection is identified in the surgical specimens of the SCC tumor, which may be associated with the pathogenesis (3). Radical surgery is the mainstay of treatment, but no standard treatment strategy has been established for unresectable EJSCC. The Cancer Genome Atlas (TCGA) project found that the gastric cancer patients

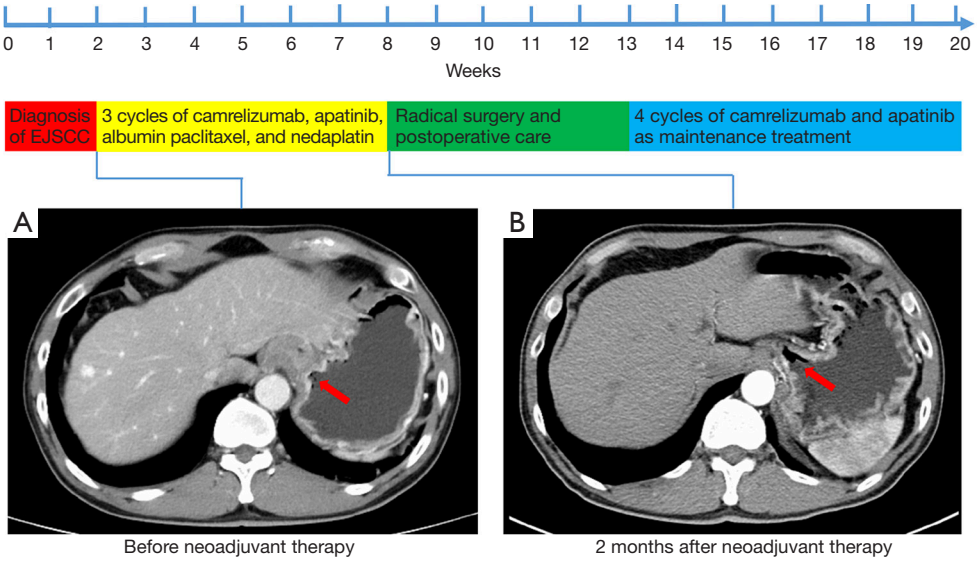

Figure 1 The timeline of the whole treatment and the CT scans. (A) An initial enhanced CT scan found a locally advanced, potentially unresectable EGJ mass (red arrow). (B) The mass on the second CT scan was significantly shrunk (red arrow). EJSCC, esophagogastric junctional squamous cell carcinoma; CT, computed tomography; EGJ, esophagogastric junctional.

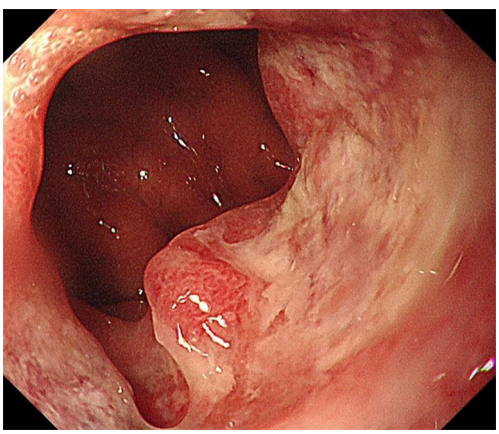

Figure 2 A gastroscope showed a circumferential and infiltrative ulcer with a blurring boundary, and it caused partial esophageal stricture.

with high microsatellite instability (MSI) or programmed death-ligand 1 (PD-L1) expression are more likely to have durable responses to programmed death-1 (PD-1) blockade with high levels of immune cell infiltration and PD-L1/2 expression (4). A small number of trials have proven that first-line PD-1 blockade plus chemotherapy could improve the prognosis of the patients with unresectable or metastatic esophageal SCC or esophagogastric junctional (EGJ) adenocarcinoma (5,6). Besides, anti-angiogenic agents can enhance anti-cancer efficacy of PD-1 blockade in several mechanisms (7). Whereas, it lacks enough clinical experience of neoadjuvant strategy for EJSCC. This is the first reported case with EJSCC who achieved a partial remission (PR) after neoadjuvant PD-1 blockade, vascular endothelial growth factor receptor 2 (VEGFR-2) inhibitor plus chemotherapy. We present the following case in accordance with the CARE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-789/rc).

Case presentation

A 64-year-old man complaint recurrent chocking after having meals for over 3 months, with the symptoms of sour regurgitation, belching and abdominal distention. He had no abdominal pain, nausea or vomiting. His body mass index (BMI) was 20.7 kg/m^2. He denied any chronic or hereditary disease. The patient had no habit of alcohol or tobacco use. The tumor markers were all within normal levels. An enhanced abdominal computed tomography (CT) scan on 17th August 2021 found a locally advanced, potentially unresectable EGJ mass (Siewert type II) (*Figure 1*). A gastroscope showed a circumferential and infiltrative ulcer (~3 cm in length, and 39–41 cm down from the incisors), which caused mild esophageal stricture (*Figure 2*), and the pathological biopsy report confirmed

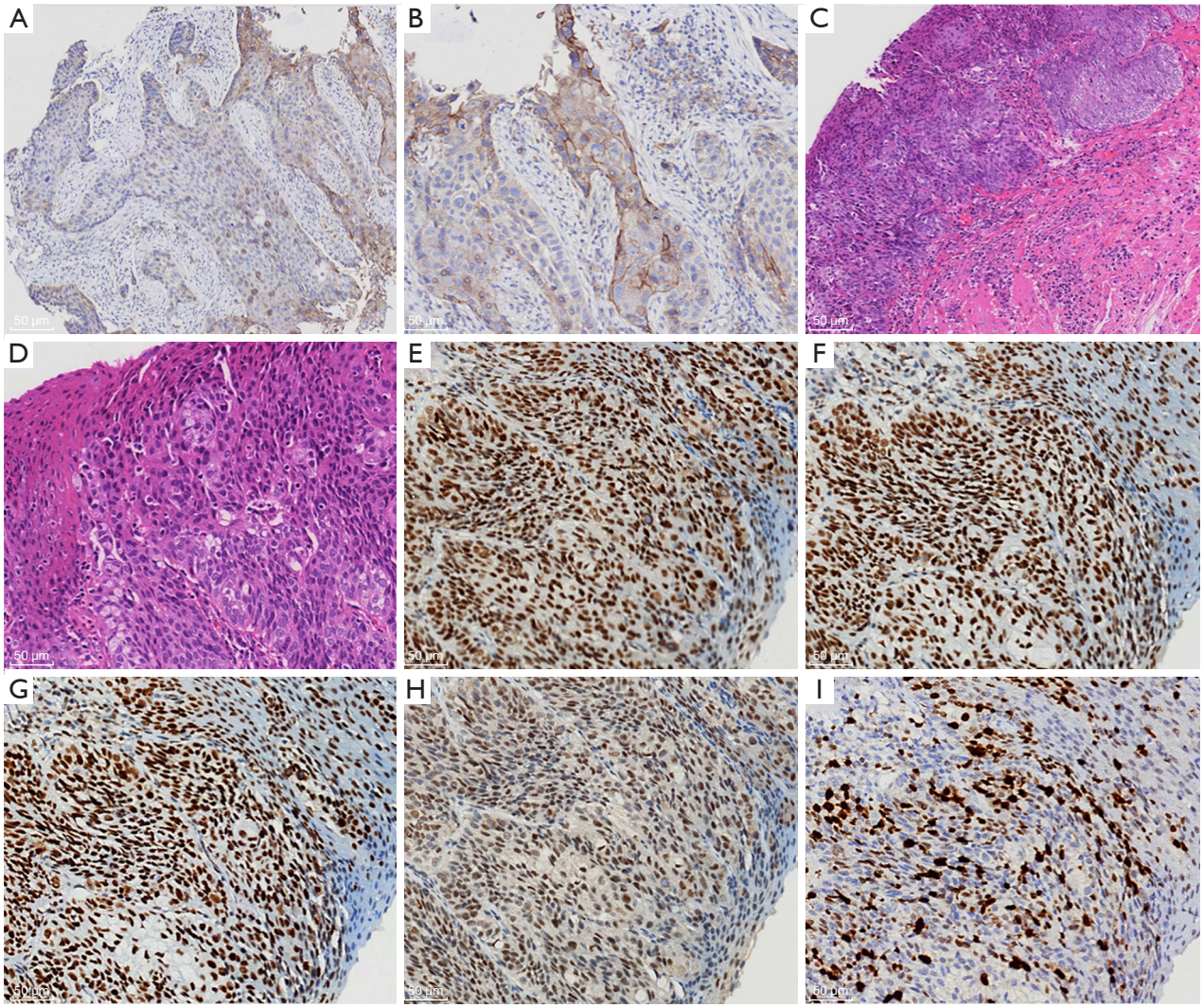

Figure 3 IHC staining of the specimens. (A) Positivity of IHC staining in the biopsy specimens for PD-L1 with PD-L1 CPS of 30 (×100). (B) Positivity of IHC staining for PD-L1 (×200). (C) H&E staining in the resected specimens exhibited SCC (×100). (D) H&E staining (×200). (E) Positivity of IHC staining for MLH1 (×200). (F) Positivity of IHC staining for MSH2 (×200). (G) Positivity of IHC staining for MSH6 (×200). (H) Positivity of IHC staining for PMS2 (×200). (I) The Ki-67 was 60% (×200). IHC, immunohistochemical; PD-L1, programmed death-ligand 1; CPS, combined positive score; H&E, hematoxylin and eosin; SCC, squamous cell carcinoma; MLH1, mutL protein homolog 1; MSH2, mutS homolog 2; MSH6, mutS homolog 6; PMS2, postmeiotic segregation increased 2.

SCC with PD-L1 combined positive score (CPS) of 30 (*Figure 3*). The patient had no financial burden, then he received three courses of neoadjuvant camrelizumab (a PD-1 blockade) (200 mg, intravenous infusion for one day), apatinib (a VEGFR-2 inhibitor) (750 mg, oral take for three consecutive days), albumin paclitaxel (200 mg, intravenous infusion for one day) and nedaplatin (70 mg, intravenous infusion for one day). He was well tolerant without any adverse event. Over two months later, a further abdominal CT scan on 27th October 2021 revealed that the tumor had been significantly shrunk, which indicated a PR had been achieved (*Figure 1*). Afterwards, total gastrectomy, distal esophagectomy and abdominal D2 lymphadenectomy were performed on 10th November 2021, and surgical margins were negative. A Borrmann type III tumor (approximately 0.5 cm in diameter) was found on the cardia, and the gastric serosal layer was intact. The pathology of the resected specimen verified a highly differentiated submucosal

SCC without any lymph node metastasis (pT2N0M0), and immunohistochemical (IHC) staining were positive for MLH1 (mutL protein homolog 1), MSH2 (mutS homolog 2), MSH6 (mutS homolog 6), PMS2 (postmeiotic segregation increased 2), P53, and the Ki-67 was 60% (*Figure 3*), and the fluorescent in situ hybridization (FISH) was negative for EBV. The patient recovered well after surgery, and he has been treated with another four cycles of camrelizumab and apatinib as maintenance treatment since 16th December 2021, and he does not have any severe adverse event except mild hypothyroidism. There is no tumor recurrence until 10th June 2022 after surgery.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

Gastric SCC is less than 2% among all gastric cancers. A study based on National Cancer Database (NCDB) revealed that 85% of gastric SCC occurred on the gastric cardia (mainly Siewert type II carcinoma), and it had worse survival compared with gastric adenocarcinoma (1). One possible etiology in some specific gastric SCC cases is EBV infection (3), whereas, the FISH showed no EBV infection in this patient. Surgical resection of stage II–III EJSCC is the main option, and it needs rigorous preoperative assessment including endoscopy, abdominal CT, contrast esophagography and positron emission tomography-CT (PET-CT) to evaluate the tumor staging and its resectability. Total gastrectomy or proximal gastrectomy with distal esophagectomy is the most commonly used surgical procedure by gastrointestinal or thoracic surgeons (8). Besides, it needs more evidences on the extent of esophageal and gastric resection and the necessity of mediastinal lymph node dissection (9,10). There is a significant trend towards minimal invasive surgery, which has a much faster recovery after surgery. Perigastric D2 lymphadenectomy is required for the eradication of the tumor cells. Moreover, Kosugi *et al.* (11) reported that 38% of the EJSCC patients developed mediastinal lymph node metastasis, and an upper or middle mediastinal lymphadenectomy was recommended for the EJSCC patients whose tumor length was ≥5.4 cm. While, another retrospective study found that there was no significant difference in the rate of mediastinal lymph node metastasis between the patients with EJSCC (22.9%) and the patients with EGJ adenocarcinoma (13.9%), and the perigastric lymph node metastasis preceded the mediastinal lymph node metastasis, only the splenic hilar (No. 10) lymph node dissections were associated with the outcomes (10).

Unfortunately, over half of the patients with EJSCC have the symptom of mild or severe dysphagia, and they are initially diagnosed at an advanced stage such as tumor infiltration of the serous layer or excessively high tumor-free margin, so their potential resectable rates are as low as 43.5% (1). And there are several major concerns on the surgical plan of the tumors on EGJ: the difficulty of either open or laparoscopic surgery, the resection range of the surgery, the possibility of via transthoracic approach, the eradication rate of the tumor cells, the risk of the postoperative complications such as anastomotic leakage, the survival benefit that the patients could achieve. Therefore, it is very necessary to have a multi-disciplinary team (MDT) discussion preoperatively.

In terms of neoadjuvant therapy, it is intended to validate the chemo-sensitivity, shrink the primary tumor and increase the R0 resection rate (12). Sometimes, negative upper margin is difficult to obtain via transabdominal approach, neoadjuvant therapy can help us minimize the range of the tumor, as to facilitate the whole operation. Nevertheless, only about 10% patents with gastric SCC underwent neoadjuvant chemotherapy or radiotherapy before surgery (1), and there is the possibility that neoadjuvant therapy fails as a tumor progression due to the insensitivity. As a result, the median overall survival (OS) of the patients with unresectable EJSCC is only 8.9 months, and the data regarding the neoadjuvant therapy of EJSCC is quite little. The TCGA research found that gastric cancer patients with a high MSI or PD-L1 expression are more likely to have durable responses to PD-1 blockade (4). In the recent years, perioperative targeted therapies and immunotherapy are introduced to maximize the objective response rate (ORR) and to improve the OS (13,14). The KEYNOTE-590 has confirmed that pembrolizumab plus chemotherapy of cisplatin and 5-FU could provide superior OS (12.4 *vs.* 8.8 months), progression free survival (PFS) (6.3 *vs.* 5.8 months) *vs.* chemotherapy alone in the patients with advanced esophageal and EGJ cancer (15). The recent CheckMate-648/649 trial has proven that nivolumab plus chemotherapy as a first-line treatment could prolong OS of the patients with gastric or EGJ adenocarcinoma and

advanced esophageal SCC, irrespective of the status of PD-L1 (5,16). Similarly, the ESCORT-1 trial has demonstrated that the combination of camrelizumab and chemotherapy significantly improved OS (15.3 *vs.* 12.0 months) and PFS (6.9 *vs.* 5.6 months) of the patients with advanced or metastatic esophageal SCC (6). Based on these positive results, PD-1 blockade plus chemotherapy becomes a promising treatment with satisfactory response rates of 45–70% (5,6,15,16). The FLOT-4 and RESOLVE trials have also shown that two or three regimens as neoadjuvant chemotherapy for EGJ cancer are effective and tolerable (17,18). The FLOT-4 trial showed that perioperative docetaxel, oxaliplatin, leucovorin and fluorouracil improved OS in locally advanced, resectable gastric or EGJ adenocarcinoma (17). Moreover, RESOLVE trial found that perioperative SOX (S-1 and oxaliplatin) could improve 3-year disease-free survival rate of the patients with locally advanced gastric or EGJ adenocarcinoma compared with postoperative XELOX (capecitabine and oxaliplatin), and perioperative SOX had an increased R0 resection rate of 92.9% (18). Accordingly, first-line neoadjuvant or perioperative therapy has an advantage of tumor downstaging, and the synergistic anticancer effects of the different combinatorial regimens remain to be studied.

On the other hand, primary or acquired resistance to PD-1 blockade can reduce the efficacy. Anti-angiogenesis therapy is associated with 'normalization' of the tumor microenvironment (TME) and has the potential to reverse therapeutic resistance to PD-1 blockade (19). Thus, PD-1 blockade combined with anti-angiogenesis have shown more clinical benefit than PD-1 blockade or anti-angiogenic monotherapy (7), they can improve anti-tumor efficacy and prolong survival in various solid tumors, and FDA has approved combinations of PD-1 blockade with vascular endothelial growth factor (VEGF)/VEGFR inhibitor in hepatocellular carcinoma and renal cell carcinoma. There are several ongoing or completed clinical trials focusing on the efficacy of PD-1 blockade and VEGF/VEGFR inhibitor with or without other regimens on esophageal, gastric and EGJ carcinoma, and these outcomes are encouraging (*Table 1*). A retrospective study has shown that PD-1 blockade with VEGFR-2 inhibitor exhibits an ORR of 26.3% for the patients with unresectable EGJ cancer (20). We have performed IHC staining of PD-L1 for the biopsy tissue with the CPS of 30. Therefore, we underwent perioperative camrelizumab, apatinib plus chemotherapy, and eventually radical surgery was successfully performed following a PR of the disease. The patient has been surviving for over 10 months since initial diagnosis. In addition, this combined treatment was safe and manageable without severe adverse effect.

Combinations of PD-1 blockade with VEGFR-2 inhibitor exhibits promising outcomes for the patients with EGJ carcinoma. However, there are some limitations in our research: first, the tumors on EGJ are divided into Siewert type I, II and III based on their locations, we need to confirm the therapeutic effect on different types of EJSCC; second, neoadjuvant treatment using two or more regimens have higher risk of severe adverse effects, especially for the malnourished or elderly patients. Thus, this strategy may not be suitable for all cases; third, the patient should be followed up in the future to determine his disease-free survival and OS.

Conclusions

In conclusion, EJSCC is a very rare malignancy with a relatively poor prognosis and its treatment is quite challenging. This case provides a novel clinical experience of neoadjuvant PD-1 blockade, VEGFR-2 inhibitor plus chemotherapy for a locally advanced, potentially unresectable EJSCC from our medical center.

Table 1 Clinical trials investigating the combination effect of PD-1 blockade and VEGF/VEGFR inhibitor with or without other regimens on esophageal, gastric and EGJ carcinoma

No.	PD-1 blockades	VEGF/VEGFR inhibitors	Other regimens	Diseases	Status	Results	AEs ≥III	Phases	Country	Trial register No.
1	Camrelizumab	Apatinib	SOX (S-1 & oxaliplatin)	G/EGJ AC	Ongoing	ORR: 79.3%, DCR: 96.6%, MFR: 96.6%, pCRR: 13.8%	34.5% (hypertension, leucopenia, thrombocytopenia, diarrhea)	II–III	China	NCT04208347

Table 1 *(continued)*

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No.	PD-1 blockades	VEGF/VEGFR inhibitors	Other regimens	Diseases	Status	Results	AEs ≥III	Phases	Country	Trial register No.
2	Camrelizumab	Apatinib	SOX (S-1 & oxaliplatin)	AFP-producing, G/EGJ AC	Ongoing	–	–	II	China	NCT04609176
3	Camrelizumab	Apatinib	SOX (S-1 & oxaliplatin)	G/EGJ AC	Ongoing	–	–	II	China	NCT04792515
4	Camrelizumab	Apatinib	–	G/EGJ AC	Ongoing	–	–	III	China	NCT04342910
5	Camrelizumab	Apatinib	SOX (S-1 & oxaliplatin)	G/EGJ AC	Ongoing	–	–	II	China	NCT03878472
6	Camrelizumab	Apatinib	–	E SCC	Completed	ORR: 34.6%	44% (liver injury)	II	China	NCT03736863
7	Camrelizumab	Apatinib	CAPOX (capecitabine & oxaliplatin)	G/EGJ AC	Completed	ORR: 58.3%, OS: 14.9 months, PFS: 5.7 months	14.6–20.8% (leucopenia, thrombocytopenia, hypertension)	II	China	NCT03472365
8	Pembrolizumab	Lenvatinib	–	EGJ AC	Ongoing	–	–	I	United States	NCT05041153
9	Pembrolizumab	Lenvatinib	–	EGJ AC	Ongoing	–	–	III	United States	NCT03321630
10	Pembrolizumab	Lenvatinib	–	G AC	Ongoing	–	–	II	Japan	NCT04745988
11	Pembrolizumab	Lenvatinib	mFOLFOX (5-FU & oxaliplatin)	E SCC	Ongoing	–	–	II	United States, China, France, *et al.*	NCT04949256
12	Pembrolizumab	Lenvatinib	Paclitaxel & carboplatin, radiation	E/EGJ, AC & SCC	Ongoing	–	–	II	United States	NCT04929392
13	Pembrolizumab	Lenvatinib	–	G AC	Completed	ORR: 69%, DCR: 100%, PFS: 6.9 months	45% (hypertension, proteinuria, thrombocytopenia)	II	Japan	NCT03609359
14	Nivolumab	Ramucirumab	Rucaparib	E/G AC	Ongoing	–	–	I–II	United States	NCT03995017
15	Nivolumab	Ramucirumab	–	G/EGJ AC	Completed	ORR: 37.2%, DCR: 83.7%, PFS: 5.1 months, OS: 13.1 months	Not posted	I–II	Japan	NCT02999295
16	Pembrolizumab	Ramucirumab	Paclitaxel	G/EGJ AC	Ongoing	–	–	II	United States	NCT04069273
17	Pembrolizumab	Ramucirumab	–	G/EGJ AC	Ongoing	–	–	II	Korea	NCT04632459
18	Pembrolizumab	Ramucirumab	–	G/EGJ AC, NSCLC, biliary tract cancer	Completed	ORR: 7–30%	24% (hypertension, colitis)	I	United States, Germany, France, *et al.*	NCT02443324
19	Atezolizumab	Bevacizumab	–	G/EGJ AC	Ongoing	–	–	II	France	NCT04739202
20	Durvalumab	Ramucirumab	–	G/EGJ AC, NSCLC, hepatocellular carcinoma	Completed	Not posted	Not posted	I	United States, Germany, France, *et al.*	NCT02572687
21	Toripalimab	Apatinib	–	G/EGJ AC	Ongoing	–	–	II	China	NCT04190745

PD-1, programmed death-1; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; EGJ, esophagogastric junctional; AEs, adverse effects; E/G, esophageal/gastric; AC, adenocarcinoma; ORR, objective response rate; DCR, disease control rate; MFR, margin free rate; pCRR, pathological complete response rate; AFP, α-fetoprotein; SCC, squamous cell carcinoma; OS, overall survival; PFS, progression free survival; NSCLC, non-small cell lung cancer.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-789/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-789/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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