



Combining anti-PD-1 antibodies with surufatinib for gastrointestinal neuroendocrine carcinoma: Two cases report and review of literature

Lou-Lu Gao, Dong-Ni Gao, Hong-Tu Yuan, Wen-Qiang Chen, Jing Yang, Jie-Qiong Peng

Specialty type: Oncology

Provenance and peer review:

Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade B

Novelty: Grade B

Creativity or Innovation: Grade B

Scientific Significance: Grade A

P-Reviewer: Guo SB

Received: October 14, 2024

Revised: December 20, 2024

Accepted: February 27, 2025

Published online: April 24, 2025

Processing time: 163 Days and 1 Hours



Lou-Lu Gao, Department of Oncology, The Affiliated Hospital of Qingdao University, Qingdao 266000, Shandong Province, China

Dong-Ni Gao, Department of Oncology, Shandong Public Health Clinical Center, Jinan 250100, Shandong Province, China

Hong-Tu Yuan, Department of Pathology, Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, Jinan 250117, Shandong Province, China

Wen-Qiang Chen, Department of Cardiology, Qilu Hospital of Shandong University, Jinan 250012, Shandong Province, China

Jing Yang, Jie-Qiong Peng, Department of Oncology, Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, Jinan 250117, Shandong Province, China

Co-first authors: Lou-Lu Gao and Dong-Ni Gao.

Co-corresponding authors: Jing Yang and Jie-Qiong Peng.

Corresponding author: Jie-Qiong Peng, Department of Oncology, Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, No. 440 Jiyan Road, Jinan 250117, Shandong Province, China. 15589116608@163.com

Abstract

BACKGROUND

Gastrointestinal neuroendocrine carcinoma (GI NEC) has a low incidence rate and poor prognosis. Most patients already have metastatic disease when they are diagnosed. Platinum chemotherapy is the main means of treating metastatic GI NECs. There is a lack of effective treatment methods after chemotherapy failure. Therefore, selecting appropriate posterior-line treatment programs to improve the prognosis of patients is urgently needed.

CASE SUMMARY

A 64-year-old female was diagnosed with stage IV NEC of the rectum due to abdominal pain and rectal bleeding. After multiline chemotherapy, the condition progressed, and the patient was treated with a combination of camrelizumab and

surufatinib. The efficacy evaluation revealed partial remission (PR) and stable conditions, with the expression of the tumor marker neuron-specific enolase (NSE) returning to normal. The adverse reactions were controllable, and the overall condition was good, with weight gain achieved in the past four years. Another 51-year-old female experienced recurrence and metastasis of a duodenal NEC after surgery. After multiline chemotherapy, she received sintilimab combined with surufatinib. The curative effect fluctuated between PR and stability. During treatment, she recovered from immune-related diabetes and later died due to deterioration of her condition. During the treatment, the patient's NSE level returned to normal.

CONCLUSION

The combination of antiangiogenic targeted drugs and immunotherapy provides a new therapeutic approach for the treatment of metastatic GI-NECs.

Key Words: Gastrointestinal neuroendocrine carcinoma; Immune checkpoint inhibitors; Angiogenesis inhibitors; Combination therapy; Case report

©The Author(s) 2025. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Effective treatment options for metastatic gastrointestinal neuroendocrine carcinomas (GI-NECs) are limited after chemotherapy failure. This study presents the cases of two patients with metastatic rectal and duodenal neuroendocrine carcinomas who achieved sustained remission and long-term survival through a combination of antiangiogenic targeted therapy and anti-PD-1 immunotherapy. These cases highlight the potential of this combination as a posterior-line treatment for GI-NECs, offering new insights into their management.

Citation: Gao LL, Gao DN, Yuan HT, Chen WQ, Yang J, Peng JQ. Combining anti-PD-1 antibodies with surufatinib for gastrointestinal neuroendocrine carcinoma: Two cases report and review of literature. *World J Clin Oncol* 2025; 16(4): 102297

URL: <https://www.wjgnet.com/2218-4333/full/v16/i4/102297.htm>

DOI: <https://dx.doi.org/10.5306/wjco.v16.i4.102297>

INTRODUCTION

Originating from cells of the diffuse neuroendocrine system, neuroendocrine neoplasms (NENs) are known for often accompanying carcinoid syndrome or hormonal symptoms[1]; they can occur primarily in various organs and sites. According to the World Health Organization classification 5th edition, NENs are classified into G1-3 neuroendocrine tumors (NETs) and neuroendocrine carcinomas (NECs) based on their grade, degree of differentiation, mitotic rate, and Ki-67 index (Table 1). NECs account for 10%-20% of all NENs and are defined as poorly differentiated tumors with more than 20 mitoses/2 mm² under high-power field microscopy, as well as a Ki-67 index higher than 20%, distinguishing them from G3 NETs, which are well differentiated[2].

The incidence of NECs is 9.36/100000 per year, according to records from the SEER database. Approximately 91.3% of these cases occur primarily in the lungs. NECs of the digestive system account for 3% of these cases, and unknown primary NECs account for 2.8%. In the digestive system, the most prevalent disease site is the colon, which accounts for 26% of cases. The second highest percentage comes from pancreatic NECs, which account for 20% of all NECs. The ratio of the stomach to rectal cases is 12%, and that of the small intestine is 5%. The incidence of most gastrointestinal (GI)-NECs is less than 0.1/100000 per year, which accounts for no more than 2% of all GI malignancies. Although less prevalent, the prognosis for GI-NECs is relatively poor. Up to 60.8% of patients have metastasis at the time of diagnosis. The 5-year survival rate of advanced GI-NEC patients is 4.7%, and the median overall survival (OS) of metastatic gastric and colorectal NECs is less than 6.2 months[3].

The treatment options for NETs include somatostatin analogs, peptide receptor radionuclide therapy, and targeted therapy; however, systemic chemotherapy remains the primary approach for managing GI-NECs, particularly in cases of metastatic disease. Due to the small patient population, chemotherapeutic regimens, which are platinum-based chemotherapies[4,5], are used mainly for small-cell lung cancer patients. Etoposide plus cisplatin (EP) is the first-line treatment, with an objective response rate (ORR) of 30%-70% and a median progression-free survival (mPFS) of 7 months [6]. Etoposide + carboplatin (EC) or irinotecan + cisplatin (IP) could serve as alternatives[7,8]. For second-line treatment, there are no standard recommendations; either capecitabine plus temozolomide (CAPTEM) + bevacizumab, FOLFOX, or FOLFIRI could be an option, although their ORRs are usually approximately 15%, and the mPFS is only 4.2 months[9-12].

Evidence of effective treatment after the failure of chemotherapy has been extremely rare for decades. Recently, immunotherapy has been explored as a therapeutic option (Table 2)[13-25]. Pembrolizumab may be a solution for highly selected dMMR/MSI-H patients, who constitute a minority (10%) of GI-NEC patients[15,26]. Although a small sample size has not been confirmed in a randomized controlled trial, dual blockade of PD-L1 and CTLA-4 showed promising ORRs of 24%-44%, and the mPFS and OS were 4.8 and 7.2 months, respectively[27]. These limited clinical benefits may not be sufficient to change clinical practice; therefore, more effective measures for posterior-line treatment are urgently

Table 1 Classification and grading criteria for neuroendocrine neoplasms of the gastrointestinal tract and hepatopancreatobiliary organs

Terminology	Differentiation	Grade	Mitotic rate (mitoses/2 mm ²)	Ki-67 index
NET, G1	Well differentiated	Low	< 2	< 3%
NET, G2		Intermediate	2-20	3%-20%
NET, G3		High	> 20	> 20%
NEC, small-cell type (SCNEC)	Poorly differentiated	High	> 20	> 20%
NEC, large-cell type (LCNEC)			> 20	> 20%
MINEN	Well or poorly differentiated	Variable	Variable	Variable

NET: Neuroendocrine tumor.

needed. Anti-angiogenic drugs play an important role in tumor treatment; however, research on their use in GI-NEC cases is relatively scarce, the optimal application mode has not been clearly defined, and further exploration is needed.

Here, we report two cases with advanced rectal and duodenal NECs. Both of these patients progressed after multiple lines of chemotherapy. By combining antiangiogenic targeted therapy and anti-PD-1 immunotherapy, both patients achieved sustained remission and long-term survival, and toxicities were tolerable. Targeted antiangiogenic therapy reduces the proliferation and metastatic ability of tumor cells by inhibiting the blood supply in the tumor microenvironment, while anti-PD-1 immunotherapy enhances the recognition and attack ability of tumor cells by activating the body's immune system. The combination of this approach may effectively prolong the survival of patients, and it is hoped that it can provide an important reference for the clinical practice of posterior-line treatment of GI-NECs.

CASE PRESENTATION

Chief complaints

Case 1: Paroxysmal lower abdominal pain and intermittent rectal bleeding for more than 3 months.

Case 2: Upper abdominal pain for more than one month.

History of present illness

Case 1: In April 2020, a 64-year-old female patient visited a local hospital for more than two months due to paroxysmal lower abdominal pain and intermittent rectal bleeding. The patient entered menopause at the age of 50.

Case 2: In 2020, a 51-year-old woman with an Eastern Cooperative Oncology Group score of 0 sought medical attention at a local hospital for one week due to yellow urine accompanied by intermittent nausea and vomiting. She had no symptoms, such as abdominal pain, vomiting blood, black stool, or fever. She went through menopause at the age of 49. Mild tenderness was observed in the upper abdomen during the physical examination. Abdominal magnetic resonance imaging (MRI) and magnetic resonance cholangiopancreatography (MRCP) revealed abnormal thickening and narrowing of the lower segment of the common bile duct with intrahepatic and extrahepatic bile duct dilation. Gastroscopy revealed a large ulcerative lesion near the ascending papilla of the duodenum, with irregular swelling of the surrounding mucosa. Biopsy pathology revealed poorly differentiated duodenal cancer. On June 2, 2020, under general anesthesia, pancreaticoduodenectomy was performed for treatment.

History of past illness

They had no past medical history.

Personal and family history

They had no other relevant personal or family history.

Physical examination

Case 1 had lower abdominal tenderness and enlarged lymph nodes palpable in the left supraclavicular area.

Case 2: A surgical incision was made in the abdomen, and multiple enlarged lymph nodes were palpable in the supraclavicular region on both sides.

Laboratory examinations

Case 1: Blood tests revealed an increase in neuron-specific enolase (NSE) to 22.38 ng/mL; other tumor markers and biochemical tests revealed no abnormalities. The preliminary pathological diagnosis of the biopsy sample was poorly

Table 2 Clinical trials in gastroenteropancreatic neuroendocrine tumors using immune checkpoint inhibitors

No.	Trial name/NCT number	Phase	Interventions	Population characteristics	ORR (%) [†]	mPFS (month)	mOS (month)
1	KEYNOTE-028 NCT02054806[13]	Ib	Pemprolizumab	Cohort A7: 16 patients with PD-L1-negative, well or moderately differentiated pancreatic NETs	6.3%	4.5	37.8
				Cohort A6: 25 patients with PD-L1-positive, locally advanced or metastatic carcinoids (lung, gut, and other locations)	12%	5.5	16.2
2	KEYNOTE-158 NCT02628067[14]	II	Pemprolizumab	107 patients with heavily pretreated, well-differentiated, progressive NETs	3.7% (7.5% in pancreatic NET subgroup)	4.1	24.2
3	NCT02939651[15]	II	Pemprolizumab	29 patients with advanced G3 NETs/NECs (48% patients had GI primaries) progressing on platinum-based chemotherapy	3.4% (1 patient)	8.86	20.43
4	PLANET NCT03043664[16]	Ib/II	Pemprolizumab + Lanreotide Depot	22 patients with nonresectable, recurrent or metastatic, well or moderately differentiated GEP-NETs	0.045% (39% stable disease, 52% progressive disease)	5.04	28.6
5	NCT03136055[17]	II	Pembrolizumab/Pembrolizumab + Chemotherapy (Irinotecan/Paclitaxel)	36 patients with extrapulmonary poorly differentiated neuroendocrine carcinomas (28% in Pem-only and 73% in Pem + chemo)	7%; 5%	1.8; 2	7.8; 4.8
6	NCT02955069[18]	II	Spartalizumab	32 patients with well-differentiated GI NETs, 33 patients with pancreatic NETs, 21 patients with poorly-differentiated GEP-NECs	3.1%, 3.0%, and 4.8%, respectively	3.8 in well-differentiated NETs; 1.8 in NECs	23.4 in well-differentiated NETs; 6.8 in NECs
7	DART SWOG 1609 NCT02834013[19]	II	Ipilimumab + Nivolumab	32 patients, of whom 15 with GI-NENs and 6 with lung-NENs	Overall: 25%; 44% in nonpancreatic high-grade NEC and 0% in low-intermediate grade tumors	4	11
8	CA209-538 NCT02923934[20]	II	Ipilimumab + Nivolumab	29 patients with advanced, any grade NENs (including atypical bronchial carcinoid and high-grade pan-NENs)	43% of patients with pan-NENs achieved an objective response	4.8 (in whole cohort)	14.8 (in whole cohort)
9	NCT03074513[21]	II	Atezolizumab + Bevacizumab	40 patients with advanced, progressive grade 1 to 2 NETs (20 with pancreatic NETs and 20 with extra-pancreatic NETs)	20% in the pancreatic NET cohort; 15% in the extra-pancreatic NET cohort	19.6 and 14.9, respectively	-
10	DUNE NCT03095274[22]	I	Durvalumab + Tremelimumab	123 patients with advanced or metastatic GEP/Lung NENs or NENs of unknown primary	11.1% in lung NENs (cohort 1), 0% in G1-2 GI NETs (cohort 2), 6.3% in G1-2 pancreatic NETs (cohort 3), 9.1% in G3 GEP-NENs (cohort 4)	5.6, 5.8, 5.5 and 2.4, respectively	Not reached, 29.5, 23.8, 5.9, respectively

11	NCT03167853[23]	Ib	Toripalimab	40 patients with NENs (of whom 9 with pan-NENs)	13.0% in GI NENs, 22.2% in pan-NENs, 37.5% in nondigestive NENs	15.4 (for TMB-high subgroup), 2.1 (for TMB-low subgroup)	Not reached (for TMB-high subgroup), 227 (for TMB-low subgroup)
12	NET-001/NET-002 NCT03278405 NCT03278379[24]	II	Avelumab	27 patients with GEP NENs or from bronchial primary, (10 G2-3 NETs in NET-001, 17 NECs in NET-002)	0% (33% stable disease)	3.3	14.2
13	AVENEC NCT03352934[25]	II	Avelumab	60 patients with G3 NET ($n = 22$) or NEC ($n = 38$) of any origin	20% (9 stable disease, 3 partial response)	2.1	4.2
14	CABOAVENEC NCT05289856[25]	II	Avelumab + Cabozantinib	19 patients (12 with G3 NET, 7 with NEC)	47.4%	12.1	-

¹The objective response rate of some trials were assessed by irRECIST criteria.

NEC: Neuroendocrine carcinoma; NET: Neuroendocrine tumor; ORR: Objective response rate; mPFS: Median progression-free survival; OS: Overall survival.

differentiated rectal carcinoma. Pathology revealed that a mixed cancer composed of large and small cells was positive for Syn expression and negative for CgA expression through IHC staining. The Ki-67 positivity rate was 80%, while CD56 expression was positive (Figure 1A). Genetic testing revealed mutations in *KRAS*, *APC*, and *TP53*, whereas *NRAS* and *BRAF* showed wild-type status and microsatellite stability.

Case 2: Blood, tumor marker level and biochemical tests revealed no abnormalities. Postoperative pathology revealed poorly differentiated MiNEC, with an ulcerative mass of 2.8 cm × 2.5 cm × 0.7 cm that penetrated the entire duodenal wall. No cancer was found at the cut edge, and lymph node metastasis was observed in 2/7 of the adjacent pancreas and in 6/7 of the mesentery. IHC results revealed partial positive Syn and positive CgA, Ki-67, and CD56 expression. Postoperative histopathological consultation revealed mixed gonadal NEC (MANEC), with poorly differentiated adenocarcinoma found in 30% of the tissue (Ki-67 index of 80%) and small cell components found in 70% of the tissue (Ki-67 index of 90%) (Figure 1B).

Imaging examinations

Case 1: Fibrocolonoscopy revealed a circumferential irregular neoplasm at the rectum, located 8-14 cm away from the anal margin (Figure 1C). The preliminary pathological diagnosis of the biopsy sample was poorly differentiated rectal carcinoma. The computed tomography (CT) scan results revealed irregular thickening of the rectal wall along with multiple enlarged lymph nodes in the pelvic cavity, abdomen, and left neck region (Figure 1D). A PET-CT scan revealed an abnormal hypermetabolic rectal neoplasm with a maximum standardized uptake value (SUV_{max}) of 8.45. Multiple enlarged and fused lymph nodes were detected adjacent to the bilateral iliac vessels in the pelvic cavity as well as in the retroperitoneum, with an SUV_{max} of 16.59. Local involvement of the right ureter was noted, with dilation of the upper ureter and right renal pelvis accompanied by hydronephrosis and impaired right renal function. A metastatic lymph node with an SUV_{max} of 10.24 was identified in the left supraclavicular region (Figure 1E).

Case 2: Abdominal MRI and MRCP were performed, revealing abnormal thickening and luminal stenosis of the lower common bile duct along with dilation of the intra- and extrahepatic bile ducts. Gastroscopy revealed a large ulcer-like lesion near the papilla of the ascending duodenum with irregular swelling of the surrounding mucosa. However, chest and abdominal CT scans revealed extensive relapse with multiple enlarged lymph nodes in the retroperitoneum, abdominal cavity, mediastinum, and bilateral supraclavicular regions.

MULTIDISCIPLINARY EXPERT CONSULTATION

The patients were eligible to receive advanced first-line treatment.

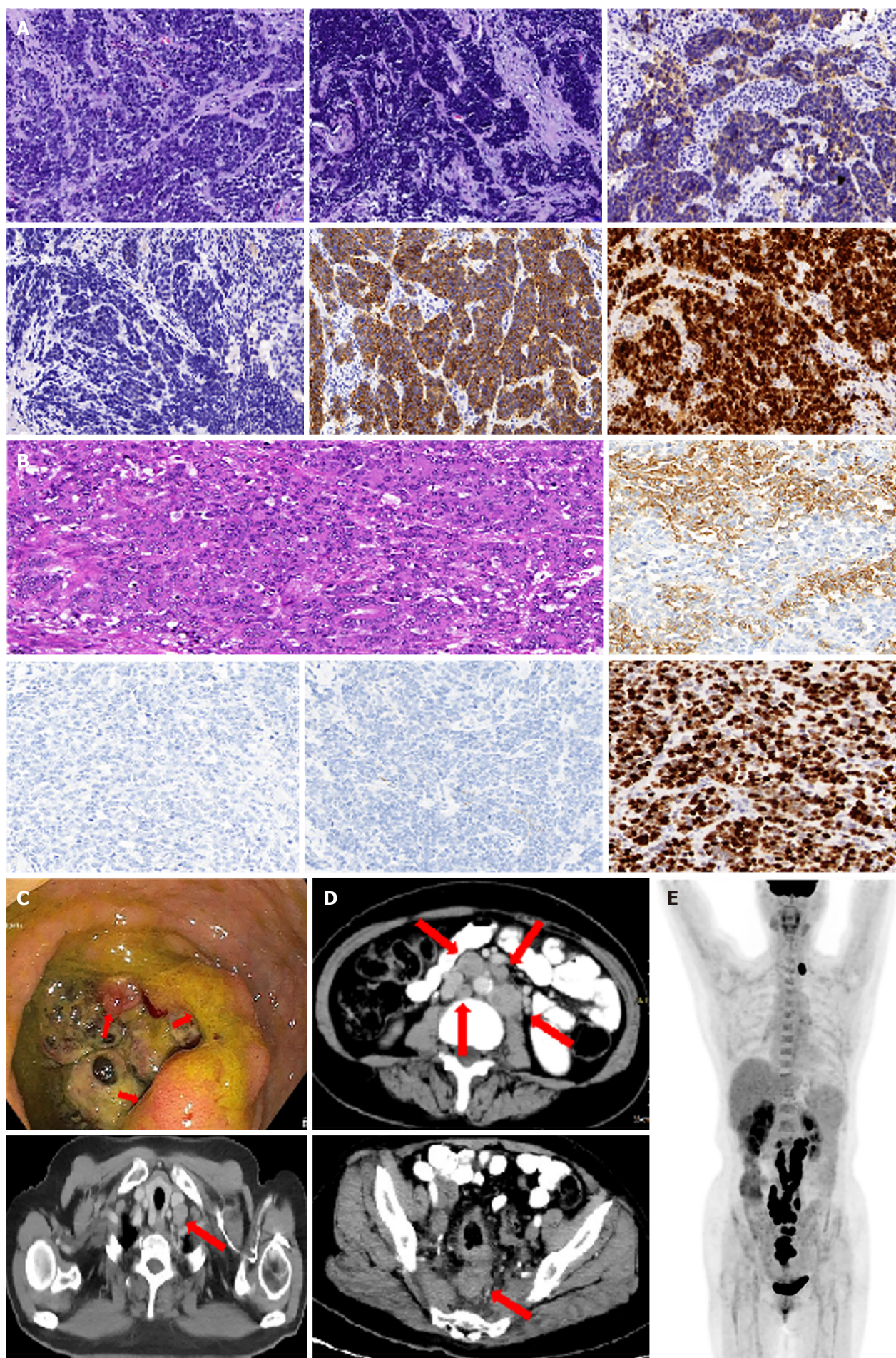
FINAL DIAGNOSIS

Case 1

The patient was diagnosed with cT3N3M1 stage IV rectal NEC.

Case 2

The patient was diagnosed with duodenal mixed adenoneuroendocrine carcinoma, with widespread recurrence and



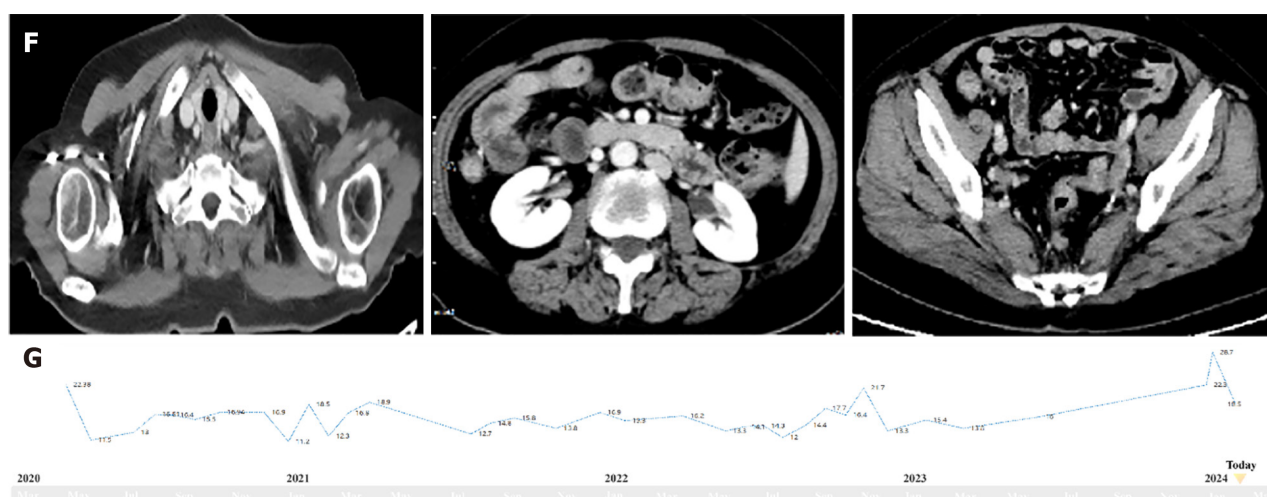


Figure 1 Imaging examination, laboratory examination for cases. A: HE staining revealed poorly differentiated atypical cells with mixed large and small cells; the scale bar at the bottom right represents 1 cm. Immunohistochemistry of Syn, CgA, CD56 and ki-67; B: Pathological assessment of surgical tissue slides: HE staining revealed poorly differentiated ulcerous mixed neuroendocrine/neuroendocrine carcinoma (MiNEC), with a ratio of 30% poorly differentiated adenocarcinoma to MiNEC; C: Colonoscopy revealed a circumferential rectal neoplasm with an irregular shape; D: Computed tomography (CT) at diagnosis revealed irregular thickening of the rectal wall with uneven enhancement and multiple enlarged nodes in the pelvic cavity, abdomen, and left neck; E: PET/CT at diagnosis revealed hypermetabolic nodes in the pelvic cavity, abdomen, and left neck; F: CTs after 11 cycles of camrelizumab and surufatinib revealed partial remission; the sizes of both the primary rectal lesion and the lymph nodes had decreased (more than 30%); G: Dynamics of NSE during the treatment process.

lymph node metastasis in the retroperitoneum, abdominal cavity, mediastinum, and bilateral supraclavicular regions.

TREATMENT

Case 1

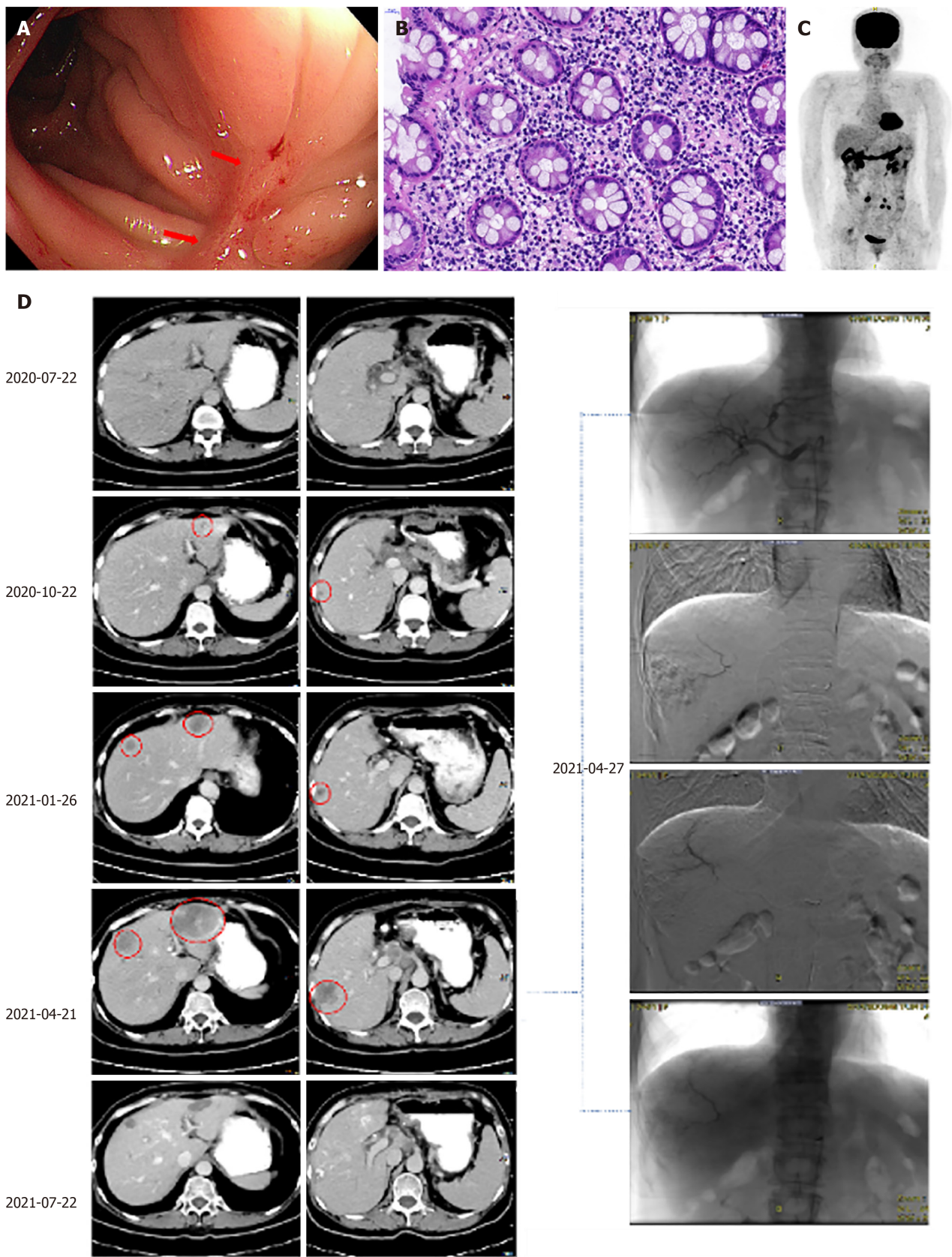
From May to August 2020, the patient began four cycles of systemic treatment with etoposide and cisplatin. After two cycles, the efficacy was evaluated as partial remission (PR) according to RECIST 1.1[28]; the efficacy evaluation after the fourth cycle of chemotherapy revealed disease progression (PD). Subsequently, second-line treatment was initiated with CAPTEM and bevacizumab. After 4 cycles of treatment, the condition stabilized, with partial progression. However, after two cycles of treatment with capecitabine plus oxaliplatin and bevacizumab, the disease continued to progress, and symptoms worsened.

Owing to the lack of a standard treatment plan for the posterior line of gastrointestinal NECs, we cautiously chose to use combination therapy consisting of the anti-PD-1 monoclonal antibody camrelizumab and the small-molecule antiangiogenic tyrosine kinase inhibitor (TKI) surufatinib (camrelizumab 200 mg d1, q3w; surufatinib 250 mg po qd). After 4 and 6 cycles of treatment, the efficacy was evaluated as a PR, with a significant reduction in the primary lesion and lymph nodes. After 8 and 11 cycles, the efficacy was evaluated as stable disease (SD) (Figure 1F). After three treatment cycles, the NSE levels returned to normal (Figure 1G). During the treatment period, the patient experienced grade II diarrhea and a mild rash, which were relieved by adjusting the dosage of sunitinib and supportive therapy. Fiber colonoscopy re-examination did not reveal any tumors on the rectal mucosa, and biopsy revealed chronic inflammation with lymphocyte infiltration, indicating complete remission of the primary rectal lesions (Figure 2A and B). The second PET-CT scan in January 2022 revealed no abnormal metabolism in the rectum or left supraclavicular area. There are still several enlarged lymph nodes behind the peritoneum, but the SUV_{max} has decreased (Figure 2C).

Case 2

Starting in July 2020, systemic chemotherapy (etoposide 0.1 g d1-5, carboplatin AUC = 6, q3-w) was administered. After 4 cycles, the disease progressed, and liver metastasis occurred. Irinotecan combined with raltitrexed was used for 3 cycles of treatment, but the disease continued to progress. CT scans revealed increased liver metastasis, and XELOX + bevacizumab was used for 3 cycles of treatment. CT scans still indicated PD; however, the patient's general condition worsened, and the patient refused to undergo another biopsy for personal reasons.

In January 2021, systemic treatment with sintilimab and surufatinib (sintilimab 200 mg q3w; surufatinib 250 mg po qd) was administered. In April 2021, due to the progression of liver metastasis, hepatic artery chemoembolization (TACE) was performed. The efficacy evaluation for treatment cycles 3 and 6 revealed a PR, whereas the assessment after cycles 9 and 12 revealed SD (Figure 2D). In the 10th cycle, the patient went to the hospital due to progressive fatigue and sudden loss of consciousness. Biochemical examination revealed that her blood glucose level was 49.6 mmol/L and that her urinary ketone body level was positive. The patient was diagnosed with hyperosmolar nonketotic diabetic coma. Patients with type I diabetes related to immunotherapy were further assessed and recovered after supportive and insulin treatments. The patient continued with the original treatment plan for 14 cycles, and the overall condition improved, with



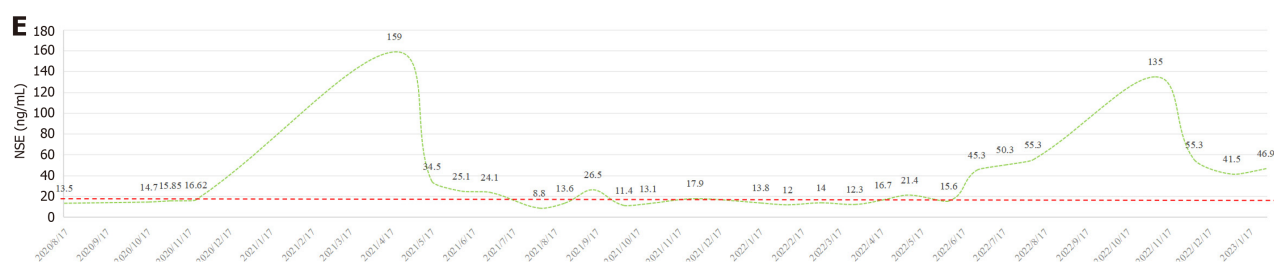


Figure 2 Imaging and laboratory tests of these cases and the course of TACE treatment of the patient in case 2. A: Colonoscopy revealed scar-like changes in the original rectal lesion with distorted surrounding mucosa; B: Microscopy of the biopsy sample revealed chronic inflammation with lymphocyte infiltration; C: PET/CT revealed no hypermetabolic uptake in the rectum or left neck, with several residual lymph nodes in the abdomen. Computed tomography (CT) at diagnosis revealed irregular thickening of the rectal wall with uneven enhancement and multiple enlarged nodes in the pelvic cavity, abdomen, and left neck; D: CT images at 1 month after surgery, 4 cycles (PD) of etoposide + carboplatin, 3 cycles (PD) of irinotecan + raltitrexed, and 3 cycles (PD) of xelox + bevacizumab. Sintilimab + surufatinib (ICI-TKI) continuous treatment (TACE of hepatic metastasis 2021-04-27); E: Dynamics of NSE during the treatment process.

NSE levels returning to normal (Figure 2E). In August 2022, a CT scan revealed an enlarged liver metastasis and a right adrenal metastasis. Owing to the presence of duodenal adenocarcinoma in the tumor, the original treatment plan included albumin-bound paclitaxel (300 mg every 3 weeks) for 4 cycles of treatment. The liver metastasis still progressed, but the patient acknowledged that the overall condition was good, tolerated the current treatment, and had a high quality of life (QoL). Chemotherapy was refused, and the patient chose to continue with the combination of sorafenib and sintilimab (right adrenal artery, right inferior phrenic artery, and hepatic artery embolizations were performed in December 2022) (Figure 3A).

OUTCOME AND FOLLOW-UP

Case 1

In November 2023, the latest CT assessment revealed PD. The combined treatment regimen, consisting of an immune checkpoint inhibitor (ICI) and surufatinib, has been consistently administered for a duration of 33 months (Figure 3B). By February 2024, nearly four years after the initial diagnosis, the patient continues to exhibit a favorable overall clinical status with a satisfactory QoL and an additional increase in body weight of 4 kg.

Case 2

In February 2023, the last efficacy evaluation after 24 months of ICI-TKI combination therapy revealed SD (Figure 3C). Owing to the deterioration of the patient's general condition and refusal to undergo further antitumor treatment, the local hospital provided symptomatic supportive treatment. Eventually, the patient passed away three months later.

DISCUSSION

NEC has a low incidence rate and is highly heterogeneous, so accurate diagnosis is the primary challenge in NEC management. Early detection is hindered by the lack of production or secretion of hormones by a large proportion of extrapulmonary NECs. Localized late-stage and metastatic GI-NECs often induce local and systemic symptoms similar to those of other malignant tumors in the digestive tract. It is also difficult to distinguish GI-NECs from other common malignant tumors in the corresponding area *via* radiological imaging or endoscopic examination. More importantly, NEC tumors are often mixed with glandular or squamous components, making them prone to diagnostic errors[29,30]. Therefore, histopathological morphology, IHC staining, and sufficient sampling are crucial for obtaining an accurate diagnosis.

Case 1 was confirmed to have rectal NEC, a mixed large- and small-cell subtype. While the small-cell subtype is dominant in lung NECs, the large-cell subtype is more prevalent in GI NECs. Both subtypes share a similar mutation landscape, although the prognosis of large-cell NECs is superior to that of small-cell NECs[18]. Up to 40% of NECs have other components mixed into a tumor[17,18]. According to the definition, a diagnosis of MiNEC is assigned if the ratio of each component is at least 30%. Adenocarcinoma, squamous cell carcinoma, or low-grade neoplasms are common causes. The adeno-mixture is also named MANEC. Case 2 was diagnosed with a 30% adenocarcinoma component in the tumor, which corresponds to her partial positivity of Syn. Duodenal NECs are commonly localized at the ampulla of Vater; their incidence is quite low, and MANECs of the duodenum are even rarer. Thus, statistics are lacking, and incidences are mostly presented as case reports[31]. With respect to the criteria of the pathological report, the ratio, differentiation, and Ki-67 index of each component should be described separately[4] to help determine the therapeutic approach. According to the pathological report, both of the components in Case 2 exhibited poorly differentiated carcinomas, and both had a high Ki-67 index, indicating the complexity of the case.

and immune suppression, thereby promoting tumor development. The mutated state of *KRAS* (such as *KRAS/STK11* and *KRAS/p53*) can affect the tumor microenvironment and immune checkpoint inhibition, potentially leading to immune suppression or an inflammatory tumor microenvironment[35]. TP53 is the most commonly mutated gene in human cancers, with a mutation rate of over 50% in at least 20 tumor types. Targeted mutation of p53 to restore wild-type activity is highly important for the treatment of cancers with high mutation frequencies[36].

Like common gastrointestinal malignancies, curative surgery and adjuvant chemotherapy (with or without radiation therapy) are the standard treatments for early invasive gastrointestinal NEC[4]. Platinum-containing systemic chemotherapy is the fundamental treatment for both large- and small-cell subtypes of metastatic GEP-NECs. The NORDIC study suggested that NECs with higher Ki-67 indices have higher response rates to platinum but are more prone to relapse than those with lower Ki-67 indices[6]. Options for posterior-line treatment are limited. There is no consensus on the best treatment for MANECs. In addition to chemotherapy for EP, EC, and IP, accommodating both components seems reasonable when assigning regimens[31].

ICIs may act through multiple mechanisms, such as recovering exhausted immune cells in the tumor microenvironment[37], and have been approved to treat a variety of malignancies, especially in the dMMR/MSI-H/TMB-H population[38,14]. Camrelizumab and sintilimab are both anti-PD-1 monoclonal antibodies that were approved by the CFDA in 2021 for treating metastatic esophageal and gastric cancer carcinomas[14,39]. They have tolerable side effects and are relatively affordable. However, current studies have indicated that monotherapy with ICIs has limited ORRs in unselected extrapulmonary NECs (Table 2); this may be because NECs are usually not 'hot' tumors with moderate TMB and stable microsatellite status[40]. Nevertheless, the effect of immunotherapy does not necessarily depend on the biomarkers above[41], so it may still be an option.

Small-molecule antiangiogenic TKIs that have multiple targets are considered to act through various mechanisms, such as suppressing tumor angiogenesis and reducing the tumor blood supply, and they play important roles in the posterior-line treatment of many solid tumors[42,43]. In NENs, sunitinib and lenvatinib have been approved for the treatment of metastatic G2-3 NETs[44,45]. Surufatinib is an antiangiogenic TKI that has been approved by the CFDA for the treatment of locally advanced or metastatic, nonfunctional, well-differentiated (G1, G2) nonpancreatic and pancreatic NETs that are not amenable to surgical resection[46]. Surufatinib works by inhibiting tumor angiogenesis as well as stimulating innate immunity; however, for NECs, there is still a lack of evidence of efficacy[47]. When used in combination, antiangiogenic TKIs are believed to normalize the microvascular structure in the tumor microenvironment, making it easier for immune cells to infiltrate the tumor, reducing hypoxia, and regulating immune cells. TKIs can alter the composition of tumor-infiltrating lymphocytes, increase the CD8⁺ T-cell response and CD45RO⁺ memory T cells, and synergistically inhibit tumors with ICIs, thereby increasing the effectiveness of immunotherapy[48]. A combination of anti-PD-1/PD-L1 immunotherapy and antiangiogenic TKIs has been applied in the systemic treatment of many solid tumors, such as sintilimab, camrelizumab, apatinib, and anlotinib, as well as in hepatocellular cell carcinoma, renal cell carcinoma, and gastrointestinal tract (GI-tract) adenocarcinoma[49-51]. However, the toxicity of combination therapy cannot be ignored. This may be due to changes in the immune environment caused by antiangiogenic TKIs, leading to an excessive immune response to ICIs. This is usually manifested as the cumulative effect of two treatments, such as gastrointestinal toxicity, skin toxicity, immunogenic pneumonia, and immunogenic hepatitis. Dose adjustments are often needed, and the efficacy can still be maintained after adjustment[48].

There are certain limitations of this article due to the nature of case reports, as they provide only limited evidence for clinical practice, the sample size is insufficient, and there is a lack of universality. Therefore, further exploration is needed.

CONCLUSION

In summary, compared with other common gastrointestinal malignancies, GI-NECs are rare and invasive, with a poorer prognosis for patients with metastatic GI-NECs. We hope that in the future, relevant research will further verify the efficacy and safety of anti-PD-1 immunotherapy combined with antiangiogenic targeted drugs in the treatment of GI-NECs, explore the relationship between biomarkers and the clinical response that needs to be evaluated, and predict patients' response to combination therapy. In addition, in-depth research on the mechanism of this combination therapy and its impact on the tumor microenvironment will help reveal its potential therapeutic advantages and improve patient prognosis.

ACKNOWLEDGEMENTS

We are very grateful for the patients' willingness to share those case.

FOOTNOTES

Author contributions: Gao LL, Gao DN, and Peng JQ wrote the draft of the manuscript; Yang J and Peng JQ polished the manuscript; and Yuan HT, Chen WQ, and Peng JQ prepared figures; all authors commented on the previous versions of the manuscript; all authors read and approved the final manuscript. Gao LL and Gao DN contributed equally to this work as co-first authors. Peng JQ and Yang J are the co-corresponding authors of this paper. During the hospitalization of the two patients in this paper, these two authors were respectively responsible for the treatment and nursing work. The two authors jointly monitored the two patients and jointly provided information

and data in the final article. The contributions of the two authors to this paper are equivalent. With the collective consent of all authors, Peng JQ and Yang J serve as co-corresponding authors.

Informed consent statement: The patient had signed the Informed consent form.

Conflict-of-interest statement: No potential conflict of interest was reported by the author(s).

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Open Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <https://creativecommons.org/licenses/by-nc/4.0/>

Country of origin: China

ORCID number: Wen-Qiang Chen 0000-0002-0350-1383; Jie-Qiong Peng 0000-0001-7724-7886.

S-Editor: Qu XL

L-Editor: A

P-Editor: Yu HG

REFERENCES

- 1 Ito T, Lee L, Jensen RT. Treatment of symptomatic neuroendocrine tumor syndromes: recent advances and controversies. *Expert Opin Pharmacother* 2016; **17**: 2191-2205 [PMID: 27635672 DOI: 10.1080/14656566.2016.1236916]
- 2 Nagtegaal ID, Odze RD, Klimstra D, Paradis V, Rugge M, Schirmacher P, Washington KM, Carneiro F, Cree IA; WHO Classification of Tumours Editorial Board. The 2019 WHO classification of tumours of the digestive system. *Histopathology* 2020; **76**: 182-188 [PMID: 31433515 DOI: 10.1111/his.13975]
- 3 Dasari A, Mehta K, Byers LA, Sorbye H, Yao JC. Comparative study of lung and extrapulmonary poorly differentiated neuroendocrine carcinomas: A SEER database analysis of 162,983 cases. *Cancer* 2018; **124**: 807-815 [PMID: 29211313 DOI: 10.1002/cncr.31124]
- 4 Garcia-Carbonero R, Sorbye H, Baudin E, Raymond E, Wiedenmann B, Niederle B, Sedlackova E, Toumpanakis C, Anlauf M, Cwikla JB, Caplin M, O'Toole D, Perren A; Vienna Consensus Conference participants. ENETS Consensus Guidelines for High-Grade Gastroenteropancreatic Neuroendocrine Tumors and Neuroendocrine Carcinomas. *Neuroendocrinology* 2016; **103**: 186-194 [PMID: 26731334 DOI: 10.1159/000443172]
- 5 Mitry E, Baudin E, Ducreux M, Sabourin JC, Rufié P, Aparicio T, Aparicio T, Lasser P, Elias D, Duvillard P, Schlumberger M, Rougier P. Treatment of poorly differentiated neuroendocrine tumours with etoposide and cisplatin. *Br J Cancer* 1999; **81**: 1351-1355 [PMID: 10604732 DOI: 10.1038/sj.bjc.6690325]
- 6 Sorbye H, Welin S, Langer SW, Vestermark LW, Holt N, Osterlund P, Dueland S, Hofslie E, Guren MG, Ohrling K, Birkemeyer E, Thiis-Evensen E, Biagini M, Gronbaek H, Soveri LM, Olsen IH, Federspiel B, Assmus J, Janson ET, Knigge U. Predictive and prognostic factors for treatment and survival in 305 patients with advanced gastrointestinal neuroendocrine carcinoma (WHO G3): the NORDIC NEC study. *Ann Oncol* 2013; **24**: 152-160 [PMID: 22967994 DOI: 10.1093/annonc/mds276]
- 7 Frizziero M, Spada F, Lamarca A, Kordatou Z, Barriuso J, Nuttall C, McNamara MG, Hubner RA, Mansoor W, Manoharan P, Fazio N, Valle JW. Carboplatin in Combination with Oral or Intravenous Etoposide for Extra-Pulmonary, Poorly-Differentiated Neuroendocrine Carcinomas. *Neuroendocrinology* 2019; **109**: 100-112 [PMID: 30703770 DOI: 10.1159/000497336]
- 8 Yamaguchi T, Machida N, Morizane C, Kasuga A, Takahashi H, Sudo K, Nishina T, Tobimatsu K, Ishido K, Furuse J, Boku N, Okusaka T. Multicenter retrospective analysis of systemic chemotherapy for advanced neuroendocrine carcinoma of the digestive system. *Cancer Sci* 2014; **105**: 1176-1181 [PMID: 24975505 DOI: 10.1111/cas.12473]
- 9 Welin S, Sorbye H, Sebjornsen S, Knappskog S, Busch C, Oberg K. Clinical effect of temozolomide-based chemotherapy in poorly differentiated endocrine carcinoma after progression on first-line chemotherapy. *Cancer* 2011; **117**: 4617-4622 [PMID: 21456005 DOI: 10.1002/cncr.26124]
- 10 Hadoux J, Malka D, Planchard D, Scoazec JY, Caramella C, Guigay J, Boige V, Lebouilleux S, Burtin P, Berdelou A, Loriot Y, Duvillard P, Chougnat CN, Déandréis D, Schlumberger M, Borget I, Ducreux M, Baudin E. Post-first-line FOLFOX chemotherapy for grade 3 neuroendocrine carcinoma. *Endocr Relat Cancer* 2015; **22**: 289-298 [PMID: 25770151 DOI: 10.1530/ERC-15-0075]
- 11 Hentic O, Hammel P, Couvelard A, Rebours V, Zappa M, Palazzo M, Maire F, Goujon G, Gillet A, Lévy P, Ruszniewski P. FOLFIRI regimen: an effective second-line chemotherapy after failure of etoposide-platinum combination in patients with neuroendocrine carcinomas grade 3. *Endocr Relat Cancer* 2012; **19**: 751-757 [PMID: 22940375 DOI: 10.1530/ERC-12-0002]
- 12 Pavel M, Öberg K, Falconi M, Krenning EP, Sundin A, Perren A, Berruti A; ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. Gastroenteropancreatic neuroendocrine neoplasms: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2020; **31**: 844-860 [PMID: 32272208 DOI: 10.1016/j.annonc.2020.03.304]
- 13 Mehnert JM, Bergsland E, O'Neil BH, Santoro A, Schellens JHM, Cohen RB, Doi T, Ott PA, Pishvaian MJ, Puzanov I, Aung KL, Hsu C, Le Tourneau C, Hollebecque A, Élez E, Tamura K, Gould M, Yang P, Stein K, Piha-Paul SA. Pembrolizumab for the treatment of programmed death-ligand 1-positive advanced carcinoid or pancreatic neuroendocrine tumors: Results from the KEYNOTE-028 study. *Cancer* 2020; **126**: 3021-3030 [PMID: 32320048 DOI: 10.1002/cncr.32883]
- 14 Marabelle A, Fakih M, Lopez J, Shah M, Shapira-Frommer R, Nakagawa K, Chung HC, Kindler HL, Lopez-Martin JA, Miller WH Jr, Italiano A, Kao S, Piha-Paul SA, Delord JP, McWilliams RR, Fabrizio DA, Aurora-Garg D, Xu L, Jin F, Norwood K, Bang YJ. Association of tumour

- mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study. *Lancet Oncol* 2020; **21**: 1353-1365 [PMID: [32919526](#) DOI: [10.1016/S1470-2045\(20\)30445-9](#)]
- 15 **Vijayvergia N**, Dasari A, Deng M, Litwin S, Al-Toubah T, Alpaugh RK, Dotan E, Hall MJ, Ross NM, Runyen MM, Denlinger CS, Halperin DM, Cohen SJ, Engstrom PF, Strosberg JR. Pembrolizumab monotherapy in patients with previously treated metastatic high-grade neuroendocrine neoplasms: joint analysis of two prospective, non-randomised trials. *Br J Cancer* 2020; **122**: 1309-1314 [PMID: [32152503](#) DOI: [10.1038/s41416-020-0775-0](#)]
 - 16 **Morse M**, Halperin DM, Uronis HE, Hsu DS, Hurwitz H, Bolch E, Warren D, Haley S, John L, Moyer A, Rushing CN, Niedzwiecki D. Phase Ib/II study of pembrolizumab with lanreotide depot for advanced, progressive gastroenteropancreatic neuroendocrine tumors (PLANET). *J Clin Oncol* 2021; **39**: 369-369 [DOI: [10.1200/jco.2021.39.3_suppl.369](#)]
 - 17 **Raj N**, Chan JA, Wang SJ, Aggarwal RR, Calabrese S, DeMore A, Fong L, Grabowsky J, Hope TA, Kolli KP, Mulvey CK, Munster PN, Perez K, Punn S, Reidy-Lagunes D, Von Fedak S, Zhang L, Bergsland EK. Pembrolizumab alone and pembrolizumab plus chemotherapy in previously treated, extrapulmonary poorly differentiated neuroendocrine carcinomas. *Br J Cancer* 2023; **129**: 291-300 [PMID: [37208512](#) DOI: [10.1038/s41416-023-02298-8](#)]
 - 18 **Yao James C**, Fazio, Nicola, Pavel Marianne E, Strosberg Jonathan R, Bergsland Emily, Ruzsniwski Philippe, Voi Maurizio, Wu Cassandr, Degtyarev Evgeny, Aimone Paola, Singh Simron. ElevatioN:NET-201 An Open-Label Phase II Study to Evaluate the Efficacy and Safety of PDR001 in Patients with Advanced or Metastatic, Well-Differentiated, Non-Functional NET of Pancreatic, Gastrointestinal (GI), or Thoracic Origin or Poorly-Differentiated. *Pancreas* 2018; **47**: 360-360
 - 19 **Wagner MJ**, Othus M, Patel SP, Ryan C, Sangal A, Powers B, Budd GT, Victor AI, Hsueh CT, Chugh R, Nair S, Leu KM, Agulnik M, Sharon E, Mayerson E, Plets M, Blanke C, Streicher H, Chae YK, Kurzrock R. Multicenter phase II trial (SWOG S1609, cohort 51) of ipilimumab and nivolumab in metastatic or unresectable angiosarcoma: a substudy of dual anti-CTLA-4 and anti-PD-1 blockade in rare tumors (DART). *J Immunother Cancer* 2021; **9** [PMID: [34380663](#) DOI: [10.1136/jitc-2021-002990](#)]
 - 20 **Klein O**, Kee D, Nagrial A, Markman B, Underhill C, Michael M, Jackett L, Lum C, Behren A, Palmer J, Tebbutt NC, Carlino MS, Cebon J. Evaluation of Combination Nivolumab and Ipilimumab Immunotherapy in Patients With Advanced Biliary Tract Cancers: Subgroup Analysis of a Phase 2 Nonrandomized Clinical Trial. *JAMA Oncol* 2020; **6**: 1405-1409 [PMID: [32729929](#) DOI: [10.1001/jamaoncol.2020.2814](#)]
 - 21 **Halperin DM**, Liu S, Dasari A, Fogelman D, Bhosale P, Mahvash A, Estrella JS, Rubin L, Morani AC, Knafl M, Overeem TA, Fu SC, Solis LM, Parra Cuentas E, Verma A, Chen HL, Gite S, Subashchandrabose P, Dervin S, Schulze K, Darbonne WC, Yun C, Wistuba II, Futreal PA, Woodman SE, Yao JC. Assessment of Clinical Response Following Atezolizumab and Bevacizumab Treatment in Patients With Neuroendocrine Tumors: A Nonrandomized Clinical Trial. *JAMA Oncol* 2022; **8**: 904-909 [PMID: [35389428](#) DOI: [10.1001/jamaoncol.2022.0212](#)]
 - 22 **Capdevila J**, Hernando J, Teule A, Lopez C, Garcia-Carbonero R, Benavent M, Custodio A, Garcia-Alvarez A, Cubillo A, Alonso V, Carmona-Bayonas A, Alonso-Gordoa T, Crespo G, Jimenez-Fonseca P, Blanco M, Viudez A, La Casta A, Sevilla I, Segura A, Llanos M, Landolfi S, Nuciforo P, Manzano JL. Durvalumab plus tremelimumab for the treatment of advanced neuroendocrine neoplasms of gastroenteropancreatic and lung origin. *Nat Commun* 2023; **14**: 2973 [PMID: [37221181](#) DOI: [10.1038/s41467-023-38611-5](#)]
 - 23 **Lu M**, Zhang P, Zhang Y, Li Z, Gong J, Li J, Li J, Li Y, Zhang X, Lu Z, Wang X, Zhou J, Peng Z, Wang W, Feng H, Wu H, Yao S, Shen L. Efficacy, Safety, and Biomarkers of Toripalimab in Patients with Recurrent or Metastatic Neuroendocrine Neoplasms: A Multiple-Center Phase Ib Trial. *Clin Cancer Res* 2020; **26**: 2337-2345 [PMID: [32086343](#) DOI: [10.1158/1078-0432.CCR-19-4000](#)]
 - 24 **Chan DL**, Rodriguez-Freixinos V, Doherty M, Wasson K, Iscoe N, Raskin W, Hallet J, Myrehaug S, Law C, Thawer A, Nguyen K, Singh S. Avelumab in unresectable/metastatic, progressive, grade 2-3 neuroendocrine neoplasms (NENs): Combined results from NET-001 and NET-002 trials. *Eur J Cancer* 2022; **169**: 74-81 [PMID: [35504244](#) DOI: [10.1016/j.ejca.2022.03.029](#)]
 - 25 **Weber M**, Apostolidis L, Krug S, Rinke A, Gruen B, Michl P, Gress T, Wagner D, Roth W, Mettler E, Ruckes C, Galle P, Fottner C. 1185MO Activity and safety of avelumab alone or in combination with cabozantinib in patients with advanced high grade neuroendocrine neoplasias (NEN G3) progressing after chemotherapy. The phase II, open-label, multicenter AVENEC and CABOAVENEC trials. *Ann Oncol* 2023; **34**: S702 [DOI: [10.1016/j.annonc.2023.09.718](#)]
 - 26 **Shah MH**, Goldner WS, Benson AB, Bergsland E, Blaszkowsky LS, Brock P, Chan J, Das S, Dickson PV, Fanta P, Giordano T, Halfdanarson TR, Halperin D, He J, Heaney A, Heslin MJ, Kandeel F, Kardan A, Khan SA, Kuvshinov BW, Lieu C, Miller K, Pillarisetty VG, Reidy D, Salgado SA, Shaheen S, Soares HP, Soulen MC, Strosberg JR, Sussman CR, Trikalinos NA, Uboha NA, Vijayvergia N, Wong T, Lynn B, Hochstetler C. Neuroendocrine and Adrenal Tumors, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* 2021; **19**: 839-868 [PMID: [34340212](#) DOI: [10.6004/jnccn.2021.0032](#)]
 - 27 **Patel SP**, Mayerson E, Chae YK, Strosberg J, Wang J, Konda B, Hayward J, McLeod CM, Chen HX, Sharon E, Othus M, Ryan CW, Plets M, Blanke CD, Kurzrock R. A phase II basket trial of Dual Anti-CTLA-4 and Anti-PD-1 Blockade in Rare Tumors (DART) SWOG S1609: High-grade neuroendocrine neoplasm cohort. *Cancer* 2021; **127**: 3194-3201 [PMID: [33882143](#) DOI: [10.1002/cncr.33591](#)]
 - 28 **Eisenhauer EA**, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009; **45**: 228-247 [PMID: [19097774](#) DOI: [10.1016/j.ejca.2008.10.026](#)]
 - 29 **Li Y**, Yau A, Schaeffer D, Magliocco A, Gui X, Urbanski S, Waghay R, Owen D, Gao ZH. Colorectal glandular-neuroendocrine mixed tumor: pathologic spectrum and clinical implications. *Am J Surg Pathol* 2011; **35**: 413-425 [PMID: [21317713](#) DOI: [10.1097/PAS.0b013e3182093657](#)]
 - 30 **Grossi U**, Bonis A, Carrington EV, Mazzobel E, Santoro GA, Cattaneo L, Centonze G, Gallo G, Kazemi Nava A, Romano M, Di Tanna GL, Zanusi G. Mixed adenoneuroendocrine carcinoma (MANEC) of the lower gastrointestinal tract: A systematic review with Bayesian hierarchical survival analysis. *Eur J Surg Oncol* 2021; **47**: 2893-2899 [PMID: [34052038](#) DOI: [10.1016/j.ejso.2021.05.021](#)]
 - 31 **Frizziero M**, Chakrabarty B, Nagy B, Lamarca A, Hubner RA, Valle JW, McNamara MG. Mixed Neuroendocrine Non-Neuroendocrine Neoplasms: A Systematic Review of a Controversial and Underestimated Diagnosis. *J Clin Med* 2020; **9** [PMID: [31963850](#) DOI: [10.3390/jcm9010273](#)]
 - 32 **Daskalakis K**, Karakatsanis A, Hessman O, Stuart HC, Welin S, Tiensuu Janson E, Öberg K, Hellman P, Norlén O, Ståhlberg P. Association of a Prophylactic Surgical Approach to Stage IV Small Intestinal Neuroendocrine Tumors With Survival. *JAMA Oncol* 2018; **4**: 183-189 [PMID: [29049611](#) DOI: [10.1001/jamaoncol.2017.3326](#)]
 - 33 **Korse CM**, Taal BG, Vincent A, van Velthuysen ML, Baas P, Buning-Kager JC, Linders TC, Bonfrer JM. Choice of tumour markers in patients with neuroendocrine tumours is dependent on the histological grade. A marker study of Chromogranin A, Neuron specific enolase,

- Progastrin-releasing peptide and cytokeratin fragments. *Eur J Cancer* 2012; **48**: 662-671 [PMID: 21945100 DOI: 10.1016/j.ejca.2011.08.012]
- 34 **Yachida S**, Totoki Y, Noë M, Nakatani Y, Horie M, Kawasaki K, Nakamura H, Saito-Adachi M, Suzuki M, Takai E, Hama N, Higuchi R, Hirono S, Shiba S, Kato M, Furukawa E, Arai Y, Rokutan H, Hashimoto T, Mitsunaga S, Kanda M, Tanaka H, Takata S, Shimomura A, Oshima M, Hackeng WM, Okumura T, Okano K, Yamamoto M, Yamaue H, Morizane C, Arihiro K, Furukawa T, Sato T, Kiyono T, Brosens LAA, Wood LD, Hruban RH, Shibata T. Comprehensive Genomic Profiling of Neuroendocrine Carcinomas of the Gastrointestinal System. *Cancer Discov* 2022; **12**: 692-711 [PMID: 34880079 DOI: 10.1158/2159-8290.CD-21-0669]
- 35 **Parikh K**, Banna G, Liu SV, Friedlaender A, Desai A, Subbiah V, Addeo A. Drugging KRAS: current perspectives and state-of-art review. *J Hematol Oncol* 2022; **15**: 152 [PMID: 36284306 DOI: 10.1186/s13045-022-01375-4]
- 36 **Tornesello ML**. TP53 mutations in cancer: Molecular features and therapeutic opportunities (Review). *Int J Mol Med* 2025; **55** [PMID: 39450536 DOI: 10.3892/ijmm.2024.5448]
- 37 **Wei SC**, Duffy CR, Allison JP. Fundamental Mechanisms of Immune Checkpoint Blockade Therapy. *Cancer Discov* 2018; **8**: 1069-1086 [PMID: 30115704 DOI: 10.1158/2159-8290.CD-18-0367]
- 38 **Marabelle A**, Le DT, Ascierto PA, Di Giacomo AM, De Jesus-Acosta A, Delord JP, Geva R, Gottfried M, Penel N, Hansen AR, Piha-Paul SA, Doi T, Gao B, Chung HC, Lopez-Martin J, Bang YJ, Frommer RS, Shah M, Ghori R, Joe AK, Pruitt SK, Diaz LA Jr. Efficacy of Pembrolizumab in Patients With Noncolorectal High Microsatellite Instability/Mismatch Repair-Deficient Cancer: Results From the Phase II KEYNOTE-158 Study. *J Clin Oncol* 2020; **38**: 1-10 [PMID: 31682550 DOI: 10.1200/JCO.19.02105]
- 39 **Hoy SM**. Sintilimab: First Global Approval. *Drugs* 2019; **79**: 341-346 [PMID: 30742278 DOI: 10.1007/s40265-019-1066-z]
- 40 **Sahnane N**, Furlan D, Monti M, Romualdi C, Vanoli A, Vicari E, Solcia E, Capella C, Sessa F, La Rosa S. Microsatellite unstable gastrointestinal neuroendocrine carcinomas: a new clinicopathologic entity. *Endocr Relat Cancer* 2015; **22**: 35-45 [PMID: 25465415 DOI: 10.1530/ERC-14-0410]
- 41 **Gibney GT**, Weiner LM, Atkins MB. Predictive biomarkers for checkpoint inhibitor-based immunotherapy. *Lancet Oncol* 2016; **17**: e542-e551 [PMID: 27924752 DOI: 10.1016/S1470-2045(16)30406-5]
- 42 **Jain RK**. Normalization of tumor vasculature: an emerging concept in antiangiogenic therapy. *Science* 2005; **307**: 58-62 [PMID: 15637262 DOI: 10.1126/science.1104819]
- 43 **Jain RK**. Antiangiogenesis strategies revisited: from starving tumors to alleviating hypoxia. *Cancer Cell* 2014; **26**: 605-622 [PMID: 25517747 DOI: 10.1016/j.ccell.2014.10.006]
- 44 **Faivre S**, Niccoli P, Castellano D, Valle JW, Hammel P, Raoul JL, Vinik A, Van Cutsem E, Bang YJ, Lee SH, Borbath I, Lombard-Bohas C, Metrakos P, Smith D, Chen JS, Ruszniewski P, Seitz JF, Patyna S, Lu DR, Ishak KJ, Raymond E. Sunitinib in pancreatic neuroendocrine tumors: updated progression-free survival and final overall survival from a phase III randomized study. *Ann Oncol* 2017; **28**: 339-343 [PMID: 27836885 DOI: 10.1093/annonc/mdw561]
- 45 **Capdevila J**, Fazio N, Lopez C, Teulé A, Valle JW, Tafuto S, Custodio A, Reed N, Raderer M, Grande E, Garcia-Carbonero R, Jimenez-Fonseca P, Hernando J, Bongiovanni A, Spada F, Alonso V, Antonuzzo L, Spallanzani A, Berruti A, La Casta A, Sevilla I, Kump P, Giuffrida D, Merino X, Trejo L, Gajate P, Matos I, Lamarca A, Ibrahim T. Lenvatinib in Patients With Advanced Grade 1/2 Pancreatic and Gastrointestinal Neuroendocrine Tumors: Results of the Phase II TALENT Trial (GETNE1509). *J Clin Oncol* 2021; **39**: 2304-2312 [PMID: 33945297 DOI: 10.1200/JCO.20.03368]
- 46 **Syed YY**. Surufatinib: First Approval. *Drugs* 2021; **81**: 727-732 [PMID: 33788183 DOI: 10.1007/s40265-021-01489-y]
- 47 **Koumarianou A**, Kaltsas G. Surufatinib - a novel oral agent for neuroendocrine tumours. *Nat Rev Endocrinol* 2021; **17**: 9-10 [PMID: 33128026 DOI: 10.1038/s41574-020-00439-0]
- 48 **Fukumura D**, Kloepper J, Amoozgar Z, Duda DG, Jain RK. Enhancing cancer immunotherapy using antiangiogenics: opportunities and challenges. *Nat Rev Clin Oncol* 2018; **15**: 325-340 [PMID: 29508855 DOI: 10.1038/nrclinonc.2018.29]
- 49 **Finn RS**, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, Kudo M, Breder V, Merle P, Kaseb AO, Li D, Verret W, Xu DZ, Hernandez S, Liu J, Huang C, Mulla S, Wang Y, Lim HY, Zhu AX, Cheng AL; IMbrave150 Investigators. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. *N Engl J Med* 2020; **382**: 1894-1905 [PMID: 32402160 DOI: 10.1056/NEJMoa1915745]
- 50 **Galle PR**, Finn RS, Qin S, Ikeda M, Zhu AX, Kim TY, Kudo M, Breder V, Merle P, Kaseb A, Li D, Mulla S, Verret W, Xu DZ, Hernandez S, Ding B, Liu J, Huang C, Lim HY, Cheng AL, Ducreux M. Patient-reported outcomes with atezolizumab plus bevacizumab versus sorafenib in patients with unresectable hepatocellular carcinoma (IMbrave150): an open-label, randomised, phase 3 trial. *Lancet Oncol* 2021; **22**: 991-1001 [PMID: 34051880 DOI: 10.1016/S1470-2045(21)00151-0]
- 51 **Motzer R**, Alekseev B, Rha SY, Porta C, Eto M, Powles T, Grünwald V, Hutson TE, Kopyltsov E, Méndez-Vidal MJ, Kozlov V, Alyasova A, Hong SH, Kapoor A, Alonso Gordo A, Merchan JR, Winquist E, Maroto P, Goh JC, Kim M, Gurney H, Patel V, Peer A, Procopio G, Takagi T, Melichar B, Rolland F, De Giorgi U, Wong S, Bedke J, Schmidinger M, Dutkus CE, Smith AD, Dutta L, Mody K, Perini RF, Xing D, Choueiri TK; CLEAR Trial Investigators. Lenvatinib plus Pembrolizumab or Everolimus for Advanced Renal Cell Carcinoma. *N Engl J Med* 2021; **384**: 1289-1300 [PMID: 33616314 DOI: 10.1056/NEJMoa2035716]



Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

Telephone: +1-925-3991568

E-mail: office@baishideng.com

Help Desk: <https://www.f6publishing.com/helpdesk>

<https://www.wjgnet.com>

