World Journal of

Gastroenterology

Contents

Contents

ABOUT COVER

AIMS AND SCOPE

The primary aim of *World Journal of Gastroenterology* (*WJG*, *World J Gastroenterol*) is to provide scholars and readers from various fields of gastroenterology and hepatology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online. *WJG* mainly publishes articles reporting research results and findings obtained in the field of gastroenterology and hepatology and covering a wide range of topics including gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, gastrointestinal oncology, and pediatric gastroenterology.

INDEXING/ABSTRACTING

The *WJG* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Current Contents/Clinical Medicine, Journal Citation Reports, Index Medicus, MEDLINE, PubMed, PubMed Central, Scopus, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The 2023 edition of Journal Citation Reports® cites the 2022 impact factor (IF) for *WJG* as 4.3; IF without journal self cites: 4.1; 5-year IF: 5.3; Journal Citation Indicator: 0.82; Ranking: 33 among 93 journals in gastroenterology and hepatology; and Quartile category: Q2. The *WJG*'s CiteScore for 2021 is 8.3 and Scopus CiteScore rank 2022: Gastroenterology is 22/149.

RESPONSIBLE EDITORS FOR THIS ISSUE

Progress in immunotherapy for neuroendocrine neoplasm of the digestive system

Wei-Xuan Pan, Xin-Mu Zhang, Shao-Long Hao, Wei Han

Wei-Xuan Pan, Shao-Long Hao, Wei Han, Department of General Surgery, Beijing Luhe Hospital, Capital Medical University, Beijing 101100, China

Xin-Mu Zhang, Department of Liver Surgery, State Key Laboratory of Complex Severe and Rare Diseases, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100730, China

Corresponding author: Wei Han, MD, Chief Doctor, Director, Professor, Department of General Surgery, Beijing Luhe Hospital, Capital Medical University, No. 28 South Xinhua Road, Tongzhou District, Beijing 101100, China. dr-han1972@mail.ccmu.edu.cn

Abstract

Neuroendocrine neoplasms (NENs) are rare heterogeneous tumors that can develop in almost any organ, with the digestive organs, including the gastrointestinal tract and pancreas being the most commonly affected sites. Despite the fact that advances in initial therapies have progressed, there is presently no recognized effective treatment for advanced NEN. Immune checkpoint inhibitors (ICIs) have shown superior efficacy in treating several types of solid tumors. Despite their successful role in the treatment of partial NENs, such as small cell lung cancer, and Merkel cell carcinoma, the role of ICIs in most of the NENs remains limited. Nevertheless, due to their specific anti-tumor mechanisms and acceptable safety profile, ICIs are a promising avenue for further study in NENs therapy. Recent clinical trials have illustrated that combination therapy with ICI is more efficient than monotherapy, and multiple clinical trials are constantly ongoing to evaluate the efficacy and safety of these combination therapies. Therefore, the purpose of this review is to provide a comprehensive summary of the clinical progress of immunotherapy in NENs affecting the digestive system, with a specific emphasis on the application of programmed cell death protein 1/programmed death receptor ligand 1 inhibitor. Furthermore, this review has an exploration of the potential beneficiary population and the inherent value of utilizing immunotherapy in the management of NENs.

Key Words: Immunotherapy; PD-1 inhibitor; Neuroendocrine neoplasm; Neuroendocrine tumor; Neuroendocrine carcinoma; Gastrointestinal; Pancreatic

Core Tip: The application of immune checkpoint inhibitor (ICI) in neuroendocrine neoplasm (NEN) is regulated by the latest clinical practice guidelines. However, immunotherapy has achieved some breakthroughs for high-grade or advanced NENs of the digestive system, for which there is currently no effective drug therapy. In this regard, we investigated the causes of the heterogeneous efficacy of ICI in NEN with different grades, differentiation, and primary organs. This review summarizes the state-of-the-art progress and trend of clinical trials for different ICI-containing regimens in NENs of the digestive system, which will aid in the conduct of subsequent clinical trials and research of related mechanisms.

INTRODUCTION

Neuroendocrine Neoplasms (NENs) are a group of rare and heterogeneous neoplasms that may originate from cells throughout the endocrine system[1]. These tumors express neuroendocrine markers and can occur in any part of the body, with a particular prevalence in the digestive system, such as the gastrointestinal (GI) tract and hepatopancreato-biliary organs. The majority of NENs are sporadic, and the exact etiology is still unknown[2]. However, less than 5% of gastroenteropancreatic (GEP) NENs occur as hereditary neoplastic syndromes, associated with gene deletions or alterations, including multiple endocrine neoplasia type 1 associated with duodenopancreatic NENs[3,4], and the von Hippel-Lindau syndrome associated with pancreatic NENs[5].

NENs of the digestive system consist of a range of tumor types, including well-differentiated neuroendocrine tumors (NETs), poorly differentiated neuroendocrine carcinomas (NECs), and mixed neuroendocrine-non-neuroendocrine neoplasms (MiNENs), which based on the degree of NEN malignancy according to the World Health Organization (WHO) classification of tumors of the digestive system (5th edition, 2019)[6]. NETs can be further classified and graded into three categories: Neuroendocrine tumors grade 1 (NET G1; low grade), NET G2 (intermediate grade), and NET G3 (high grade). This classification is determined based on the Ki-67 proliferation index and the number of mitotic figures per 2 mm^2. NECs include large cell-type NEC (LCNEC) and small cell-type NEC (SCNEC), both of which are considered as high grades. MiNENs exhibit varying degrees of differentiation and grades because they possess both neuroendocrine and non-neuroendocrine components in a single patch of neoplastic tissue, with each component accounting for ≥ 30%.

In recent years, with widespread improvements in clinical diagnosis and treatment, including endoscopy and imaging, there has been a noticeable worldwide upward trend in the detection of early-stage and non-functioning NENs from the digestive system. NEN incidence increased 6.4 times between 1973 (1.09/100000) and 2012 (6.98/100000), according to an analysis published in 2017 and based on 64971 NEN cases from the Surveillance Epidemiology and End Results database of the National Cancer Institute[7]. According to statistics from England, the incidence of NENs was about 9/100000 in 2018, and the incidences of pancreatic and rectal NENs have increased significantly[8]. Similarly, based on Taiwanese data, the incidence of NENs in digestive organs increased from 0.15 per 100000 people in 1996 to 2.36 per 100000 people in 2015[9].

The most prevalent primary sites have also been shown to vary across different regions. In the United Kingdom, the order of frequency among all primary sites of GEP-NETs, was as follows: Small intestine (25.6%), appendix (23.6%), pancreas (17.7%), colon (9.8%), stomach (9.8%), and rectum (7.8%)[10]. In China, however, the order was different, with the pancreas (31.5%), rectum (29.6%), and stomach (27.0%) being the common sites. The small intestine (5.6%) and colon (3.0%) accounted for relatively small proportions of NENs in this region[11]. Compared with others, gallbladder NENs are more scarce and account for only 0.5% of all NENs[12]. NETs are prone to metastasis to the liver; however, the liver itself is rarely the primary site of NENs, accounting for only 0.46% of primary liver tumors[13]. Owing to the rarity of the diagnosis and a lack of valid statistics for relevant cases, the quality of published data is limited, and the epidemiology of patients with digestive MiNENs remains unknown[14].

Immune checkpoint inhibitors (ICIs) have potent, strong anti-tumor activity in the management of various cancer types. These inhibitors, which target programmed cell death protein 1 (PD-1) or programmed death receptor ligand 1 (PD-L1), are profoundly researched and widely used in tumor immunotherapy. Both PD-1 and PD-L1 targeted antibodies relieve the functional inhibition of T cells and reactivate the immune response against cancer cells. Several α-PD-1 (*e.g.*, palivizumab, nivolumab, and toripalimab) and α-PD-L1 antibodies (*e.g.*, atezolizumab and durvalumab) have been licensed by the Food and Drug Administration (FDA) for the treatment of multiple forms of tumor owing to their efficacy in clinical trials. More than 10 different cancer types have been authorized for therapy with single-agent PD-1 or PD-L1 monoclonal antibodies, with objective response rates (ORR) ranging from 15%-20%[15]. However, the PD-1 or PD-L1 axis is not the only signaling access that contributes to tumor immunosuppression, and the inhibition of this pathway alone is insufficient to effectively elicit anti-tumor immunity. Consequently, several combination immunotherapies, such as PD-1/PD-L1 antibodies combined with chemotherapy, radiotherapy, angiogenesis inhibitors, other ICIs, gut microbiota transplantation, and metabolic modulators, may improve the overall anti-tumor activity and raise the response rates (RRs) of NENs of the digestive system[16].

Herein, we comprehensively summarize the clinical application status and research progress of immunotherapy drugs, mainly PD-1 and PD-L1 inhibitors, for the treatment regimen of NENs of the digestive system, which might provide more potent and widely applicable regimens as well as direction for subsequent studies.

IMMUNOTHERAPY AND NENS OF THE DIGESTIVE SYSTEM

The use of immunotherapy to treat NENs of the digestive system is still in the clinical exploration phase and is not yet recommended as the preferred regimen. This is because available clinical trials have demonstrated low ORRs to immunotherapy using PD-1 or PD-L1 inhibitors. Currently, several immunotherapeutic strategies for NENs are undergoing clinical trials, including ICI monotherapy, dual ICI therapy, anti-angiogenesis with ICIs, and chemotherapy with ICI. Table 1 provides a summary of relevant data from the clinical trials mentioned below.

Application status of ICIs in NENs of the digestive system

According to the National Comprehensive Cancer Network Clinical Practice Guidelines of Neuroendocrine and Adrenal Tumors (version 2.2022), ICIs are not currently available as a preferred regimen for the systemic treatment of patients with unresectable locally advanced or distant metastases from NEN. In the preferred regimen, the molecularly targeted drug everolimus is more effective in advanced G1 or G2 NET. In phase III clinical research, mPFS in the everolimus group was longer than in the placebo group (11 *vs* 3.9 mo; *P* < 0.00001) and decreased recurrence rate as well as mortality by 52%[17]. Somatostatin analogs, such as octreotide and lanreotide, are mainly used in the treatment of NENs that are somatostatin receptor-positive, slow-growth as well as Ki-67 ≤ 10% and are usually combined with molecularly targeted drugs to control the symptom of functional NETs. Chemotherapy is typically the preferred treatment option for G3 NET and NEC. The ORR of cisplatin or carboplatin combined with etoposide in the treatment of advanced NECs ranged from 30.8%-63.2%, and the median overall survival (mOS) was between 8.9-12.5 mo[18,19]. Temozolomide combined with capecitabine has more efficacy in pancreatic NET (pNET) than in GI NET, and the mPFS and mOS in high-grade NET were longer than those in NEC (15.3 mo *vs* 3.3 mo; 22 mo *vs* 4.6 mo)[20].

Although most NENs have not demonstrated the greatest effectiveness, ICIs can still be used as the primary treatment for well-differentiated grade 3 NETs, extrapulmonary poorly differentiated NECs, and MiNENs. Patients with advanced tumor mutational burden-high [tumor mutational burden (TMB)-H], microsatellite instability-high (MSI-H), or mismatch repair deficiency (dMMR) tumors, as identified by an FDA-approved test performed after prior therapy, may be candidates for the PD-1 inhibitor pembrolizumab if no other appropriate options for therapy are available. For biologically favorable or unfavorable locally advanced or metastatic G3 NETs (unresectable with clinically considerable tumor burden or indication of disease progression), pembrolizumab is the primary treatment[21,22]. In the event of extrapulmonary, locoregional, unresectable, or metastatic NECs/MiNENs, pembrolizumab can also be considered for systemic therapy[21,22,23]. Nivolumab combined with ipilimumab (category 2B), which is known as a type of dual ICI therapy, is a recommended option for locally progressed or metastatic G3 NETs with unfavorable biologies[24]. Similarly, if the illness advances after chemotherapy, ipilimumab paired with nivolumab (category 2B) might also be taken into consideration for extrapulmonary poorly differentiated (LCNEC/SCNEC) or unknown primary tumors.

However, the Guidelines of the Chinese Society of Clinical Oncology for Neuroendocrine Neoplasms (version 2022) only suggest the use of ICIs as a treatment option for metastatic NECs. Specifically, pembrolizumab is recommended as a first-line treatment (category 3) or as a level-2 recommendation for the second-line treatment of metastatic NEC in patients with performance status (PS) scores of 0-2 and the presence of dMMR, MSI-H, or TMB-H (category 1A)[25]. In addition, ICIs such as ipilimumab, combined with nivolumab[24] or other ICIs[26-28], may be considered for patients with metastatic NECs who have previously received systemic therapy and continue to experience disease progression and who lack standard treatment options. For these patients, ICIs are recommended as a level-3 recommendation for second-line treatment (category 3A).

ICI monotherapy

ICI monotherapy has shown remarkably low RRs in NENs, especially in poorly differentiated ones. The Keynote-028 trial demonstrated the actual clinical outcomes of pembrolizumab monotherapy in patients who had carcinoid tumors and pNET with PD-L1 expression[29]. In the pNET cohort, 16 PD-L1-positive patients out of 106 pNET patients received pembrolizumab monotherapy with ORRs of 6.3% [95% confidence interval (CI): 0.2%-30.2%], only one patient confirmed partial response (PR), 31% developed stable disease (SD) lasting more than 6 mo, and 12-mo progression-free survival (PFS) and overall survival (OS) rates of 27% and 87%, respectively. However, studies comparing the efficiency of pembrolizumab in patients with or without PD-L1 expression reported no significant differences in the disease control rate (DCR), PFS, or OS between the two groups[30]. Among 29 patients who had experienced prior treatments, 48% and 34% had GI and pancreatic NENs, respectively. Only one patient (95%CI: 0.1-17.8%) with an esophageal LCNEC had an objective PR that persisted for 13 mo before he discontinued his participation in the study. Six patients (95%CI: 7.9-39.7%) had SDs, and DCR was 24.1%[30]. In an open-label phase II trial, pembrolizumab single-agent therapy in 107 well-differentiated NETs of the lung, appendix, small intestine, colon, rectum, or pancreas with previously failed standard treatments resulted in an ORR of only 3.7% (95%CI: 1.0-9.3). The median PFS (mPFS) was 4.1 mo (95%CI: 3.5-5.4), the estimated PFS rate at 6 mo was 39.3%, and the mOS was 24.2 mo. Among 40 patients with pancreatic NETs, 25 patients with small intestine NETs, and 18 patients with other GI NETs, only 4 patients had a PR as assessed by Response Evaluation Criteria in Advanced Solid Tumors version 1.1, including cases in the pancreas (3) and rectum (1); all of them were PD-L1 negative. It is noteworthy that the response rate in the pancreatic NETs subgroup was 7.5%[31]. In another

Table 1 Clinical trials mentioned in the review

Intervention	Study phase	Actual enrollment	NEN type of the digestive system	ORR (%)	mPFS (mo)	mOS (mo)	Ref.
Pembrolizumab	I	16	pNET	6.3	4.5	21.0	[29]
	II	29 (14 GI, 10 pancreas)	GI-NEN, pNEN	3.4	2.0	4.7	[30]
	II	107 (83 GEP)	WD NETs	3.7	4.1	24.2	[31]
Toripalimab	Ib	40 (23 GI, 9 pancreas)	GI-NEN	13.0	2.5	7.8	[32]
			pNEN	22.0			
Nivolumab	II	185 (93 GEP)	GEP-NEC	7.0	1.8	7.2	[33]
Spartalizumab	II	95 NETs (32 GI, 33 pancreas); 21 GEP-NECs	GI NET	3.1	3.8	Not estimable	[34]
			pNET	3.0			
			GEP-NEC	4.8	1.8	6.8	
Avelumab	II	27 (21 GEP)	GEP-NET	--	3.3	14.2	[35]
Nivolumab + Ipilimumab	--	34 (21 from digestive organs)	NENs	14.7	1.0	5.0 (from treatment initial); 14.0 (from diagnosis)	[36]
	II	32 (15 GI)	Non-pNETs	25.0	4.0	11.0	[37]
	II	19 (9 from digestive organs)	High-grade NENs	26.0	2.0	8.7	[38]
	II	185 (93 GEP)	GEP-NEC	14.9	1.9	5.8	[33]
	--	11	Metastatic EP-NEC (mainly of GEP origin)	--	8.5	Not reached	[39]
Durvalumab + Tremelimumab	II	123 (31 GI, 32 pancreas, 33 GEP)	G1/G2 GI-NETs	0	5.8	29.5	[40,41]
			G1/G2 pNETs	6.3	5.5	23.8	
			G3 GEP-NENs	9.1	2.4	5.9	
Atezolizumab + Bevacizumab	II	40 (20 pNET, 20 non-pNET)	pNET	20.0	19.6	30.1	[44,45]
			Non-pNET	15.0	14.9	Not reached	
Pembrolizumab + Lenvatinib	II	20 (10 GI)	GI-NEN	10.0	10.0	--	[46]
Pembrolizumab + Irinoteca/Paclitaxel	II	22 (16 GI)	GI-NEC	9.0	2.0	4.0	[47]
Nivolumab + Tezolomide	II	15 (12 evaluable and 7 GEP)	GEP-NET	25.0	--	--	[48]
Nivolumab + Cisplatin/Carboplatin	II	38 (31 GEP)	G3 NENs	54.1	5.7	13.9	[49,50]

WD: Well-differentiated; NET: Neuroendocrine tumor; NEN: Neuroendocrine neoplasm; NEC: Neuroendocrine carcinoma; GEP: Gastroenteropancreatic; SCLC: Small cell lung cancer; MCC: Merkel cell carcinoma; pNET: Pancreas NET; ORR: Objective response rate; mOS: Median overall survival; mPFS: Median progression-free survival; EP-NEC: Extrapulmonary neuroendocrine carcinoma.

multicenter phase Ib clinical trial investigating toripalimab for metastatic or recrudescent NENs where standard therapies had failed, 40 patients were enrolled. Of these, for ex-pancreatic GI-derived, pancreatic, and nondigestive NENs, the ORRs were 13.0% (3/23), 22.2% (2/9), and 37.5% (3/8), respectively[32].

The effectiveness of ICI monotherapy in treating NECs has also been proven in a number of clinical trials. In a phase II trial involving 185 patients with NECs (93 were GEP) and randomly assigned (1:1) to receive nivolumab monotherapy or nivolumab combined with ipilimumab. In the monotherapy group, the ORR at 8 wk, mPFS, and mOS were 7.2% (95%CI: 2.7-15.1), 1.8 mo (95%CI: 1.7-2.0), and 7.2 mo (95%CI: 3.7-14.1), respectively. However, these results indicated that the therapeutic effect was not ideal[33]. Spartalizumab, another anti-PD-1 agent, was evaluated in a clinical trial involving 21 patients with poorly differentiated GEP-NECs and 95 patients with metastatic G1 or G2 NETs (32 GI and 33 pancreatic), all of whom had received prior treatments for their advanced diseases. The ORR in the GI NET, pNET, and GEP-NEC groups was 3.1% (95%CI: 0.1-16.2), 3.0% (95%CI: 0.1-15.8), and 4.8% (95%CI: 0.1-23.8), respectively. In the NET cohort, the mPFS, 12-mo PFS, and OS rates were 3.8 mo, 19.5% (95%CI: 11.6-28.9), and 73.5% (95%CI: 63.0-81.4) respectively. For the GEP-NEC cohort, the respective values were 1.8 mo, 0%, and 19.1% (95%CI: 4.8-40.6)[34]. Although the efficacy of spartal-

izumab for digestive NEN treatment is limited and not worthy of further investigation, its AEs are mild and manageable. Fatigue (29.5%) and nausea (10.5%) were the most frequently reported spartalizumab-related AEs that emerged during the trial of the NET cohort; they were mainly distributed in the grade 1/2, while elevated aspartate/alanine aminotransferase levels (14.3% each) were common in the GEP NEC group[34]. Other trials, however, reported contrary conclusions regarding the use of ICI monotherapy. Two trials of avelumab monotherapy, which enrolled 27 patients in total, had 21 GEP-NET, with none achieving OR but only 33% obtaining SD. AEs related to avelumab were observed in 58% of patients, including grade 3-4 AEs in 3 cases, leading directly to trial termination[35].

The aforementioned ICI monotherapy regimens have indicated mild anti-tumor activity with neither NET nor NEN of the digestive system. Nonetheless, the AEs were manageable, which made them relatively safe and applicable under most conditions. It is speculated that the severity of adverse reactions may be correlated with the efficacy. In pembrolizumab treatment, for instance, only 21.5% of treatment-related adverse reactions occurred at grade ≥ 3, while the frequent adverse reactions were malaise (22.4%) and diarrhea (13.1%)[31]. Therefore, combination therapies to improve the efficacy of ICIs against NENs in the digestive system have emerged as a major research direction.

COMBINED IMMUNOTHERAPY FOR NENS OF THE DIGESTIVE SYSTEM

Dual ICI therapy

Cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) antibody, another type of ICI, have mechanisms of action complementary to those of PD-1 and PD-L1 antibodies. The binding of CTLA-4 and CTLA-4 antibodies to the surface of activated T cells indirectly promotes the activation and proliferation of T cell development by relieving the inhibitory effect of antigen-presenting cells on T cells. One preliminary retrospective evaluation for the treatment with ipilimumab plus nivolumab reported ORR, DCR, and mPFS of 15%, 41.2%, and one month (95%CI: 0.54-1.46 mo), respectively, in 34 patients with G3 NENs (79% NEC and 21 from digestive organs) who had previously undergone at least one cytotoxic chemotherapy regimen and, on average, two prior lines of treatment[36]. These findings suggest that dual ICI therapy has therapeutic effects on aggressive NECs that progress after chemotherapy, as well as in heavily pre-treated NENs. The S1609DART trial established the combination of ipilimumab and nivolumab as an option for extrapulmonary poorly differentiated (LCNEC/SCNEC) or unknown primary tumors. Results of the trial revealed that the ORR of 32 cases was 25% (95%CI: 13%-64%), and the median overall survival (mOS) was 11 mo. The ORR was 44% for non-pancreatic (non-p) high-grade NECs (8/18, CR = 1, PR = 7), including lung primaries[37]. Furthermore, in the following research on high-grade NENs, 19 patients were involved, of which 11% (each) were from the pancreas, gastroesophageal junction, and rectum. The ORR of this cohort was 26% (95%CI: 11-45%), the DCR was 32% (95%CI: 13%-57%), and the 6-month PFS was 32% (95%CI: 16%-61%); however, durable control was observed in patients with long-term diseases[38]. Based on the existing outcomes, Mohamed *et al*[39] conducted a retrospective study of 70 metastatic EP-NEC cases, mostly derived from GEP, of which 11 received Nivolumab in combination with Ipilimumab. The PFS (56.5 d, 47 d, and 258 d) and OS (not reached, 18.7 mo and 10.5 mo) were compared among patients treated with ICI monotherapy (8 patients), cytotoxic agents (23 patients) and dual ICI therapy. Thus, dual ICI therapy did show some improvement in high-grade NENs, in line with previous findings.

However, not all dual ICI therapies elicit a significant response or treatment effect. The final results from a prospective Phase II study of durvalumab plus tremelimumab in 123 patients with NENs who experienced disease progression and failure to respond to standard therapy administration were presented at the ENETS Annual Conference 2022. The cases were divided into four cohorts based on grading and primary sites: 27 patients with typical/atypical lung carcinoids for Cohort 1 (C1), 31 patients with G1/G2 GI-NETs for C2, 32 patients with G1/G2 pNETs for C3, and 33 patients with G3 GEP-NENs (91% NECs) for C4. The ORRs for the last three cohorts were 0%, 6.3%, and 9.1%, respectively, and the mPFSs were 5.8, 5.5, and 2.4 mo, in the same order. The median OSs were 29.5 mo, 23.8 mo, and 5.9 mo, respectively[40]. The 9-month DCRs for these cases were 22.8% (95%CI: 16.0-30.8), and 35.5% (95%CI: 20.5-53.0), 25% (95%CI: 12.6-41.7), and 6.1% (95%CI: 1.3-18.1) for C2 to C4, respectively[41]. Therefore, this study showed that the therapeutic effectiveness of dual ICI therapy in well-differentiated NENs was limited after the failure of standard treatment and had a relatively lower ORR. Only G3 GEP-NEN or NEC cases showed a modest survival benefit. In the NIPI-NEC phase II trial, 185 patients with platinum-refractory disease, including 93 patients with GEP-NEC, were enrolled. They were randomly assigned to receive nivolumab monotherapy or nivolumab plus ipilimumab, with ORR at eight weeks as the primary outcome measure. The cohort of nivolumab combined with ipilimumab in the trial demonstrated a prominent ORR of 14.9% (95%CI: 8.2-24.2) when compared to the nivolumab single-agent cohort of 7.2% (95%CI: 2.7-15.1); however, PFS was 1.9 mo (95%CI: 1.6-2.1) *vs* 1.8 mo (95%CI: 1.7-2.0), OS was 5.8 (95%CI: 3.3-7.6) *vs* 7.2 mo (95%CI: 3.7-14.1)[33]. Thus, most patients with NECs are not eligible for ICIs monotherapy, and the anti-tumor activity of dual ICIs therapy for both NETs and NECs needs further validation.

ICI combined with targeted anti-angiogenesis

Patients with refractory tumors or those who are chemo-intolerant have a high-quality option to de-chemotherapy in the form of ICIs combined with anti-angiogenic medications. Basic research has demonstrated a synergistic impact between ICIs and anti-angiogenic medications, encouraging angiogenesis in healthy tissues and boosting anti-tumor immunity [42]. Besides, anti-angiogenic targeted medications not only prevent angiogenesis in tumor tissue but also support the efficacy of ICIs by relieving the negative regulatory process of vascular endothelial growth factor (VEGF) in the immune microenvironment. They also influence lymphocyte and macrophage infiltration into tumor tissue, thereby alleviating the suppression of the tumor immune system[43].

Daniel and colleagues examined atezolizumab with bevacizumab combination therapy in G1/G2 pNET and non-pNET patients who had progressed under any previous therapy. Preliminary results showed that ORR, mPFS, and 1-year PFS of the two cohorts with 20 patients each were 20% (95%CI: 6%-44%) and 15% (95%CI: 3%-38%), and 19.6 mo (95%CI: 10.6-NR), and 14.9 mo (95%CI: 6.1-NR), 75% and 52%, respectively. These findings manifested that pNET patients might benefit more from this drug application regimen than non-pNET patients[44]. More recently, the MD Anderson Cancer Center released the final trial results showing that the ORR of the two groups remained consistent with the previous data; however, the PFS of the pNET and the non-pNET group descended to 14.9 mo (95%CI: 4.4-32.0) and 14.2 mo (95%CI: 10.2-19.6), respectively[45].

Al-Toubah *et al*[46] tested an alternative regimen, involving pembrolizumab plus lenvatinib, with efficacy in 20 patients with well-differentiated GI or thoracic NETs (including 9 of the small intestine, and 1 of cecal), and the response rate of the treatment was unsatisfactory. Among them, only one NET presented with PR, and the mPFS was 10 mo (95%CI: 5.9-14.1) in the small intestine, and the adverse effect rate was also high. Potentially related or related grade 3 AEs, were experienced by 12 patients, 14 patients required dose reduction or discontinuation of one of the drugs. Consequently, further research into this regimen was not deserved since it did not demonstrate substantial effectiveness for GI-NET. Therefore, it may be more worthwhile to delve into the safety and beneficial effects of ICIs paired with anti-angiogenesis in NECs from the digestive organs.

ICI combined with chemotherapy

Immunotherapy paired with chemotherapy has been successfully applied in the treatment of non-small cell lung cancer, gastric cancer, and esophageal cancer due to their synergistic mechanisms. Moreover, to expand the scope of application, some clinical study outcomes on the application of this sort of regimen in the NEN of the digestive system have been published.

The result of a phase II trial reported by Chan *et al*[47] revealed an unsatisfactory treatment response rate. The trial included twenty-two patients with extrapulmonary poorly differentiated NECs who had experienced disease progression after prior first-line therapy. These patients participated in a clinical trial investigating the combination of pembrolizumab and chemotherapy combination (16 of these patients had a primary GI site), 17 (77%) were treated with irinotecan, and 5 (23%) were treated with paclitaxel. The ORR was 9% among the patients, PR was achieved only in 2 cases, SD in 14% of cases, and PD in 60%. As inferred from the results, after biomarker selection, combination therapy with pembrolizumab and chemotherapy may improve treatment efficacy in cases of poorly differentiated GI-NEC.

In another phaseIIclinical study, twelve of the fifteen patients with advanced NET who were enrolled in and treated with nivolumab and temozolomide could be assessed for their response to this treatment, with the major locations being six small bowels, one pancreas, and five bronchial tubes[48]. According to the interim efficacy results, 25% of patients (3/12) had the best response of PR, 67% of patients (8/12) had SD, and one patient (8%) had PD.

The NICE-NEC study, which included 38 patients with advanced or irresectable gastroenteritis or G3 NENs of unknown origin, was the first to assess the efficacy of first-line chemotherapy plus ICIs in G3 NENs. Of these patients, 81.6% were GEP-NENs, and 68% were NECs, that received nivolumab combined with cisplatin or carboplatin[49]. The latest results, presented at the ESMO Congress 2022, confirmed the combinations had relatively promising therapeutic action, with an ORR and mPFS of survivors of 54.1% and 5.7 mo (95%CI: 5.1-9 mo), respectively[50]. Preliminary findings suggest that adding nivolumab to chemotherapy for G3 NENs has conceivable effectiveness without noticeably raising the toxicity profile of preferred standard chemotherapy.

Naturally, in certain rare circumstances, the combined effects of immunotherapy and chemotherapy may be therapeutically productive for some patients with terminal NECs, or those who have failed to respond to initial therapies. Chorath *et al*[51] reported a female case with metastatic high-grade NEC of the gallbladder who received immunochemotherapy treatment. A substantial decrease in liver metastases was observed following six cycles of comprehensive treatment with etoposide, carboplatin, nivolumab, and ipilimumab with a sustained response. However, further investigation is needed to comprehend the specific mechanisms and biomarkers that predict treatment efficacy. This survival benefit occurred in the absence of known predictive biomarkers to immunotherapy (PD-L1 status, mismatch repair status, and TMB).

Contrary to conventional perception, chemotherapy drugs can induce immunogenic tumor cells to undergo apoptosis, which mobilizes antigen-presenting cells and primes tumor-specific immune responses[52]. This fundamental principle underlies the previously described synergistic impact and the advantages of chemotherapy paired with ICIs in the application of NEN from the digestive system.

Table 2 provides an overview of ongoing clinical trials, which can be tracked to obtain the latest research progress of immunotherapies in NENs of the digestive systems.

BIOMARKERS FOR PREDICTING IMMUNOTHERAPY RESPONSE

MSI/dMMR, TMB, and PD-L1 expression are key biomarkers used to judge the potential benefit of ICIs for patients. Among these, MSI-H/dMMR, and TMB-H are independent adverse prognostic indicators[53]. However, the incidence of MSI-H/dMMR in NENs is relatively low, reported to be present in only 8 out of 152 GEP-NECs (5.3%) and only 1 in 29 G3 NETs (3.4%)[54]. TMB is the ratio of non-synonymous mutations in somatic cells per megabase pair of a certain genomic region. Although TMB is linked to the prognostic status of patients after ICIs therapy for the majority of malignancies, the selection of detecting genes will directly impact the TMB calculation's outcomes[55]. It is unlikely that there is an exact universal value that defines TMB-H in a way that can predict the benefit of ICI in all types of cancer[56]. In a number of published trials, PD-L1 positive patients treated with ICIs had a higher ORR than PD-L1 negative patients,

Table 2 Ongoing clinical trials related to immune checkpoint inhibitors in neuroendocrine neoplasms of the digestive system

Indentifier of Clinical Trails	Intervention	Study phase	Primary outcome measures	Estimated or actual enrollment	Trial status	Estimated study completion date	Condition related to NENs of the digestive system
NCT04079712	Nivolumab + Ipilimumab + Cabozantinib	II	overall response rate	30	Active, not recruiting	October 2023	NECs: Excluding SCLC and MCC
NCT03980925	Nivolumab + Platinum-doublet chemotherapy	II	OS at 12 mo	38	Active, not recruiting	December 2023	G3 NENs: GEP or unknown primary site
NCT04197310	Cabozantinib + Nivolumab	II	ORR	35	Active, not recruiting	December 2023	WD-NET: Non-pancreatic (*i.e.,* carcinoid) origin
NCT03290079	Pembrolizumab + Lenvatinib	II	ORR	28	Active, not recruiting	January 2024	NETs: WD small bowel or colon origin, including unknown primary, excluding pNENs
NCT04400474	Cabozantinib + Atezolizumab	II	ORR	93	Active, not recruiting	March 2024	WD G1/2 NET: Digestive system; G3 NEN: Excluding SCLC
NCT04579757	Surufatinib + Tislel-izumab	Ib/II	DLT, ORR	135	Active, not recruiting	June 2024	G1/2 NETs: Thoracic or GEP origins
NCT04525638	Nivolumab + 177Lu-DOTATATE	II	overall response rate	30	Recruiting	September 2024	G3 NET or NEC of GEP, lung, and unknown primary site
NCT05058651	Atezolizumab + Platinum drug (cisplatin or carboplatin) + Etoposide	II/III	OS	189	Recruiting	October 2024	NEC: Extrapulmonary
NCT05113355	Chidamide + Sintilimab	II	ORR	23	Recruiting	November 2024	High-grade NEN, advanced and metastatic
NCT04969887	Nivolumab + Ipilimumab	II	CBR, 6 mo PFS	240	Recruiting	December 2024	NECs and G3 NETs: Independent of primary site, excluding SCLC
NCT04701307	Dostarlimab + Niraparib	II	6 mo PFS, 3 mo ORR	48	Active, not recruiting	May 2025	NECs: Excluding prostate origin
NCT03475953	Avelumab + Regorafenib	I/II	Phase I: Recommended dose of regorafenib; Phase II (cohort G): CR or PR	747 (only cohort G consists of GEP-NETs)	Recruiting	December 2025	G2/3 GEP-NETs
NCT05746208	Lenvatinib + Pembrol-izumab	II	ORR	29	Not yet recruiting	July 2027	WD G3 NET: GIsite and pancreas primary
NCT05289856	Avelumab + Cabozantinib	II	DCR, CR, PR, SD	30	Recruiting	December 2025	G3 NET: Excluding MCC and SCLC
NCT05627427	Surufatinib + Sintilimab	II	PFS	60	Recruiting	December 2024	G3 NET and NEC: Metastatic and advanced
NCT05262556	NP-101 (TQ Formula) + Nivolumab + Ipilimumab	I	CR, PR, SD	10	Recruiting	December 2024	GEP-NET, GEP-NEC: Poorly differentiated

CR: Complete response; CBR: Clinical benefit rate; DCR: Disease control rate; DLT: Dose-limiting toxicity; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival; PR: Partial response; WD: Well differentiated; NET: Neuroendocrine tumor; NEN: Neuroendocrine neoplasm; NEC: Neuroendocrine carcinoma; GEP: Gastroenteropancreatic; SCLC: Small cell lung cancer; MCC: Merkel cell carcinoma; pNET: Pancreas NET; GI: gastrointestinal; G1, 2, 3: Grade 1, 2, 3.

which indicated that PD-L1 expression may be relevant to the efficacy of immunotherapy[45]. However, PD-L1 expression appears quite heterogeneous across different studies[57], even though some studies revealed no relevance between the effectiveness of ICIs and PD-L1 expression[30,31,40]. Reasons for these results may be subject to limitations due to factors such as different methods of analysis, defined cutoffs, and the freshness of biopsy tissue obtained[58]. Therefore, based on identifying the expression of PD-L1, investigate the content of other predictive biomarkers to provide patients with the best immunotherapy prediction possible.

In recent years, somatic mutation analysis of NETs has emerged as a novel approach for identification and prediction. Unlike conventional monoanalytic biomarker testing, mRNA-based liquid biopsy is a non-invasive genetic testing method. The NET transcriptome signature (NETest), a pre-spotted PCR plate that targets 51 genes, measures the amount of tumor-derived mRNA extracted from a patient's blood using PCR[59]. Compared to CGA, the diagnostic accuracy of GEP-NENs with NETest is significantly better (99% *vs* 21%-36%), and it also has good sensitivity and specificity for evaluating the course and prognosis of NENs[60]. However, despite these advancements, the gold standard for NETest has not been established in clinical practice preventing its use as a routine test for NEN and limiting its ability to completely replace biopsy procedures.

Future research should prioritize the integration of data on the circulating tumor DNA, T-cell regulatory factors, and other characteristics of NEN patients who will receive immunotherapy. By employing multidimensional and dynamic combinations of biomarkers, researchers can enhance the predictive effect and fully elucidate the potential causes of patients' poor responses to ICIs.

DISCUSSION

It is necessary for the body to trigger an appropriate anti-tumor immune response through the infiltration of immune cells into the tumor immune microenvironment (TIME). The strength of individual anti-tumor immunity depends significantly on the quantity and variety of T cells[61]. As a result, there is now broad acceptance that effector T cell plays an irreplaceable role in the anti-tumor response[62].

Malignancies that exhibit significant tumor-infiltrating lymphocyte (TIL) infiltration, high PD-L1 expression, potential genetic susceptibility, and the existence of an active anti-tumor immune response, often known as the hallmarks of "hot tumors," are more receptive to immunotherapy[63]. Although recent outcomes of clinical trials suggest that the efficacy of ICIs for NEN of the digestive system fell short of expectations, considerable TIL infiltration has been observed in various NECs, including pNECs[64]. Moreover, the likelihood that NEN will match the TIME of hot tumors increases with NEN grade. In a study of 244 patients with GEP-NEN, the G3 NEN cohort contained considerably more patients with high TILs infiltration than the G1/G2 NEN group (50% *vs* 17.1%)[65]. PD-L1-expressing GEP-NEC more frequently exhibited T cell exhaustion and an abundance of regulatory T cells than did G3-NET[66], indicating that poorly differentiated NECs are more prone to benefit from immunotherapies, particularly ICIs. Additionally, there was heterogeneity in the TIME of the primary sites of NENs. For instance, in comparison to NETs from the jejunum and ileum, the duodenum NETs had a more positive detection rate of PD-1 and immune infiltration[67]; and compared to NETs of extra-pancreatic origin, pNETs had higher expression levels of PD-1 and PD-L1, as well as more TILs[65]. At the same primary site, PD-L1 expression varies across multiple NET subtypes as well, with prior research demonstrating that the metastasis-like primary (MLP)-1 subtype expresses PD-L1 at the highest levels in pNET[68]. This illustrates the need for further research into the variations in the immune microenvironments of distinct differentiated primary sites and subtypes of NEN, which may guide the therapeutic application of ICIs and assist in selecting the best immunotherapy regimens for patients during clinical trials.In addition, probing into the processes which transform NEN with modest levels of TIL infiltration and PD-L1 expression into immunologically "hot" tumors could potentially serve as a research avenue to enhance the therapeutic effectiveness of ICIs. So far, several mechanisms have been implicated in altering the low immune state of "cold" tumors, for example, stimulating T cell priming (*e.g.*, injection of Neoepitope Cancer Vaccine), accelerating T cell expansion (*e.g.*, application of interleukin (IL)-15), and inducing T cell recruitment (*e.g.*, through the use of epigenetic modulators and chemokines), *etc*[69]. Further research is needed to evaluate the feasibility of the above treatments for NEN of the digestive system.

CONCLUSION

Due to the complexity of NENs in the digestive system, the prognosis following the failure of first-line treatment is frequently poor, and the options for subsequent treatment are constrained. ICI monotherapy for the NEN is less effective, has a shorter duration of disease control, and may only be effective in selected patients. Combination therapy may improve the efficacy of ICI treatment in certain cases. Dual immunotherapy has some effect on highly malignant NECs and may be considered after the failure of standard treatment; however, more relevant clinical studies are needed in this field. The combination of ICI and anti-angiogenic drugs has exhibited certain advantages and promising applications for advanced NETs. The combination of ICI and chemotherapy has shown some efficacy for advanced NENs and NECs; however, further studies are required to determine whether it ultimately improves patient outcomes, and how to select the best combination regimen. Additionally, several preclinical studies and clinical trials have investigated the combination of ICIs with other clinical oncology treatment modalities, including pericyte therapy (CAR-T cell therapy), cytokine therapy, oncolytic virus therapy, and cancer vaccines, but experimental data in NEN are lacking. Other strategies to modify the TME of NEN, such as enhancing T-cell homing, preventing T-cell depletion, and preserving

CD8+ T-cell immune response, are also worth investigating in conjunction with ICIs for targeted therapy[70]. TMB-H, PD-L1, and MSI-H/dMMR have been identified as biomarkers for screening patients who may benefit from immunotherapy; however, their overall predictive efficiency is limited. Further research on the immune microenvironment and the search for more predictive immunotherapy markers with higher sensitivity and specificity to guide clinical treatment are urgently needed.

Owing to the rarity of NENs of the digestive organs, most previous and ongoing clinical trials have predominantly used small samples and on small scales approaches, resulting in limited trial results on the subject. Currently, the evidence supporting the use of ICI for NENs of the digestive systems is primarily based on a small number of phase I or II studies and a few case reports. To address this limitation, it is crucial to conduct multi-center, prospective, large-sample clinical trials. Such trials can further validate the conclusions drawn from studies like those discussed here. Additionally, these trials can guide the application of ICI for the treatment of NENs from the digestive system, and provide promising ideas for future research in the field of immunotherapy.

FOOTNOTES

Author contributions: Pan WX and Zhang XM contributed equally to this work; Pan WX, Zhang XM, Hao SL, and Han W contributed to writing-review & editing; Pan WX contributed to writing-original draft, Visualization; Zhang XM and Han W contributed to supervision Zhang XM contributed to conceptualization, investigation; Han W contributed to project administration.

ORCID number: Xin-Mu Zhang 0000-0003-2979-1144; Wei Han 0000-0003-0652-6794.

REFERENCES

1   **de Mestier L**, Cros J, Neuzillet C, Hentic O, Egal A, Muller N, Bouché O, Cadiot G, Ruszniewski P, Couvelard A, Hammel P. Digestive System Mixed Neuroendocrine-Non-Neuroendocrine Neoplasms. *Neuroendocrinology* 2017; **105**: 412-425 [PMID: 28803232 DOI: 10.1159/000475527]

2   **Anlauf M**, Garbrecht N, Bauersfeld J, Schmitt A, Henopp T, Komminoth P, Heitz PU, Perren A, Klöppel G. Hereditary neuroendocrine tumors of the gastroenteropancreatic system. *Virchows Arch* 2007; **451** Suppl 1: S29-S38 [PMID: 17684762 DOI: 10.1007/s00428-007-0450-3]

3   **Marx SJ**. Recent Topics Around Multiple Endocrine Neoplasia Type 1. *J Clin Endocrinol Metab* 2018; **103**: 1296-1301 [PMID: 29897580 DOI: 10.1210/jc.2017-02340]

4   **Anlauf M**, Perren A, Klöppel G. Endocrine precursor lesions and microadenomas of the duodenum and pancreas with and without MEN1: criteria, molecular concepts and clinical significance. *Pathobiology* 2007; **74**: 279-284 [PMID: 17890894 DOI: 10.1159/000105810]

5   **Speisky D**, Duces A, Bièche I, Rebours V, Hammel P, Sauvanet A, Richard S, Bedossa P, Vidaud M, Murat A, Niccoli P, Scoazec JY, Ruszniewski P, Couvelard A; GTE Group, Groupe d'Etude des Tumeurs Endocrines. Molecular profiling of pancreatic neuroendocrine tumors in sporadic and Von Hippel-Lindau patients. *Clin Cancer Res* 2012; **18**: 2838-2849 [PMID: 22461457 DOI: 10.1158/1078-0432.CCR-11-2759]

6   **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]

7   **Dasari A**, Shen C, Halperin D, Zhao B, Zhou S, Xu Y, Shih T, Yao JC. Trends in the Incidence, Prevalence, and Survival Outcomes in Patients With Neuroendocrine Tumors in the United States. *JAMA Oncol* 2017; **3**: 1335-1342 [PMID: 28448665 DOI: 10.1001/jamaoncol.2017.0589]

8   **White BE**, Rous B, Chandrakumaran K, Wong K, Bouvier C, Van Hemelrijck M, George G, Russell B, Srirajaskanthan R, Ramage JK. Incidence and survival of neuroendocrine neoplasia in England 1995-2018: A retrospective, population-based study. *Lancet Reg Health Eur* 2022; **23**: 100510 [PMID: 36176500 DOI: 10.1016/j.lanepe.2022.100510]

9   **Chang JS**, Chen LT, Shan YS, Chu PY, Tsai CR, Tsai HJ. An updated analysis of the epidemiologic trends of neuroendocrine tumors in Taiwan. *Sci Rep* 2021; **11**: 7881 [PMID: 33846396 DOI: 10.1038/s41598-021-86839-2]

10   **Genus TSE**, Bouvier C, Wong KF, Srirajaskanthan R, Rous BA, Talbot DC, Valle JW, Khan M, Pearce N, Elshafie M, Reed NS, Morgan E, Deas A, White C, Huws D, Ramage J. Impact of neuroendocrine morphology on cancer outcomes and stage at diagnosis: a UK nationwide cohort study 2013-2015. *Br J Cancer* 2019; **121**: 966-972 [PMID: 31649320 DOI: 10.1038/s41416-019-0606-3]

11   **Fan JH**, Zhang YQ, Shi SS, Chen YJ, Yuan XH, Jiang LM, Wang SM, Ma L, He YT, Feng CY, Sun XB, Liu Q, Deloso K, Chi Y, Qiao YL. A nation-wide retrospective epidemiological study of gastroenteropancreatic neuroendocrine neoplasms in china. *Oncotarget* 2017; **8**: 71699-71708 [PMID: 29069739 DOI: 10.18632/oncotarget.17599]

12   **Niu C**, Wang S, Guan Q, Ren X, Ji B, Liu Y. Neuroendocrine tumors of the gallbladder. *Oncol Lett* 2020; **19**: 3381-3388 [PMID: 32269610 DOI: 10.3892/ol.2020.11461]

13   **Huang K**, Lan Z, Chen W, Zhang J, Wang J, Zhu H, Xu B, Zhang L, Lu T, Guo Y, Wen Z. Hepatectomy and pneumectomy combined with targeted therapy for primary hepatic neuroendocrine carcinoma: Case report and review of the literature. *Front Surg* 2022; **9**: 920276 [PMID: 35910478 DOI: 10.3389/fsurg.2022.920276]

14   **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]

15   **Cheng AL**, Hsu C, Chan SL, Choo SP, Kudo M. Challenges of combination therapy with immune checkpoint inhibitors for hepatocellular carcinoma. *J Hepatol* 2020; **72**: 307-319 [PMID: 31954494 DOI: 10.1016/j.jhep.2019.09.025]

16   **Yi M**, Zheng X, Niu M, Zhu S, Ge H, Wu K. Combination strategies with PD-1/PD-L1 blockade: current advances and future directions. *Mol Cancer* 2022; **21**: 28 [PMID: 35062949 DOI: 10.1186/s12943-021-01489-2]

17   **Yao JC**, Fazio N, Singh S, Buzzoni R, Carnaghi C, Wolin E, Tomasek J, Raderer M, Lahner H, Voi M, Pacaud LB, Rouyrre N, Sachs C, Valle JW, Fave GD, Van Cutsem E, Tesselaar M, Shimada Y, Oh DY, Strosberg J, Kulke MH, Pavel ME; RAD001 in Advanced Neuroendocrine Tumours, Fourth Trial (RADIANT-4) Study Group. Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. *Lancet* 2016; **387**: 968-977 [PMID: 26703889 DOI: 10.1016/S0140-6736(15)00817-X]

18   **Zhang P**, Li J, Zhang X, Zhou J, Wang X, Peng Z, Shen L, Lu M. Etoposide and cisplatin *vs* irinotecan and cisplatin as the first-line therapy for patients with advanced, poorly differentiated gastroenteropancreatic neuroendocrine carcinoma: A randomized phase 2 study. *Cancer* 2020; **126** Suppl 9: 2086-2092 [PMID: 32293725 DOI: 10.1002/cncr.32750]

19   **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]

20   **Rogowski W**, Wachuła E, Gorzelak A, Lebiedzińska A, Sułżyc-Bielicka V, Iżycka-Świeszewska E, Żołnierek J, Kos-Kudła B. Capecitabine and temozolomide combination for treatment of high-grade, well-differentiated neuroendocrine tumour and poorly-differentiated neuroendocrine carcinoma - retrospective analysis. *Endokrynol Pol* 2019; **70**: 313-317 [PMID: 30843182 DOI: 10.5603/EP.a2019.0010]

21   **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]

22   **Merino DM**, McShane LM, Fabrizio D, Funari V, Chen SJ, White JR, Wenz P, Baden J, Barrett JC, Chaudhary R, Chen L, Chen WS, Cheng JH, Cyanam D, Dickey JS, Gupta V, Hellmann M, Helman E, Li Y, Maas J, Papin A, Patidar R, Quinn KJ, Rizvi N, Tae H, Ward C, Xie M, Zehir A, Zhao C, Dietel M, Stenzinger A, Stewart M, Allen J; TMB Harmonization Consortium. Establishing guidelines to harmonize tumor mutational burden (TMB): in silico assessment of variation in TMB quantification across diagnostic platforms: phase I of the Friends of Cancer Research TMB Harmonization Project. *J Immunother Cancer* 2020; **8** [PMID: 32217756 DOI: 10.1136/jitc-2019-000147]

23   **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]

24   **Klein O**, Kee D, Markman B, Michael M, Underhill C, Carlino MS, Jackett L, Lum C, Scott C, Nagrial A, Behren A, So JY, Palmer J, Cebon J. Immunotherapy of Ipilimumab and Nivolumab in Patients with Advanced Neuroendocrine Tumors: A Subgroup Analysis of the CA209-538 Clinical Trial for Rare Cancers. *Clin Cancer Res* 2020; **26**: 4454-4459 [PMID: 32532787 DOI: 10.1158/1078-0432.CCR-20-0621]

25   **Le DT**, Durham JN, Smith KN, Wang H, Bartlett BR, Aulakh LK, Lu S, Kemberling H, Wilt C, Luber BS, Wong F, Azad NS, Rucki AA, Laheru D, Donehower R, Zaheer A, Fisher GA, Crocenzi TS, Lee JJ, Greten TF, Duffy AG, Ciombor KK, Eyring AD, Lam BH, Joe A, Kang SP, Holdhoff M, Danilova L, Cope L, Meyer C, Zhou S, Goldberg RM, Armstrong DK, Bever KM, Fader AN, Taube J, Housseau F, Spetzler D, Xiao N, Pardoll DM, Papadopoulos N, Kinzler KW, Eshleman JR, Vogelstein B, Anders RA, Diaz LA Jr. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. *Science* 2017; **357**: 409-413 [PMID: 28596308 DOI: 10.1126/science.aan6733]

26   **Mulvey C**, Raj NP, Chan JA, Aggarwal RR, Cinar P, Hope TA, Kolli K, Zhang L, Calabrese S, Grabowsky JA, Modarresi L, Kelly V, Stonely D, Munster PN, Reidy DL, Fong L, Bergsland EK. Phase II study of pembrolizumab-based therapy in previously treated extrapulmonary poorly differentiated neuroendocrine carcinomas: Results of Part A (pembrolizumab alone). *JCO* 2019; **37**: 363-363 [DOI: 10.1200/JCO.2019.37.4_suppl.363]

27   **Fottner C**, Apostolidis L, Ferrata M, Krug S, Michl P, Schad A, Roth W, Jaeger D, Galle PR, Weber MM. A phase II, open label, multicenter trial of avelumab in patients with advanced, metastatic high-grade neuroendocrine carcinomas NEC G3 (WHO 2010) progressive after first-line chemotherapy (AVENEC). *J Clin Oncol* 2019; **37**: 4103-4103 [DOI: 10.1200/JCO.2019.37.15_suppl.4103]

28   **Yao JC**, Strosberg J, Fazio N, Pavel ME, Ruszniewski P, Bergsland E, Li D, Tafuto S, Raj N, Campana D, Hijioka S, Raderer M, Guimbaud R, Gajate P, Pusceddu S, Reising A, Degtyarev E, Mookerjee B, Aimone P, Singh S. Activity & safety of spartalizumab (PDR001) in patients (pts) with advanced neuroendocrine tumors (NET) of pancreatic (Pan), gastrointestinal (GI), or thoracic (T) origin, & gastroenteropancreatic neuroendocrine carcinoma (GEP NEC) who have progressed on prior treatment (Tx). *Ann Oncol* 2018; **29**: viii467-viii468 [DOI: 10.1093/annonc/mdy293.001]

29   **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]

30   **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]

31   **Strosberg J**, Mizuno N, Doi T, Grande E, Delord JP, Shapira-Frommer R, Bergsland E, Shah M, Fakih M, Takahashi S, Piha-Paul SA, O'Neil B, Thomas S, Lolkema MP, Chen M, Ibrahim N, Norwood K, Hadoux J. Efficacy and Safety of Pembrolizumab in Previously Treated Advanced Neuroendocrine Tumors: Results From the Phase II KEYNOTE-158 Study. *Clin Cancer Res* 2020; **26**: 2124-2130 [PMID: 31980466 DOI: 10.1158/1078-0432.CCR-19-3014]

32   **Lu M**, Zhang P, Zhang Y, Li Z, Gong 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]

33   **Girard N**, Mazieres J, Otto J, Lena H, Lepage C, Egenod T, Smith D, Madelaine J, Gérinière L, Hajbi FE, Ferru A, Clément-Duchêne C, Madroszyk A, Desrame J, Morin F, Langlais A, Michel P, Louvet C, Westeel V, Walter T. LBA41 Nivolumab (nivo) ± ipilimumab (ipi) in pre-treated patients with advanced, refractory pulmonary or gastroenteropancreatic poorly differentiated neuroendocrine tumors (NECs) (GCO-001 NIPINEC). *Ann Oncol* 2021; **32**: S1318 [DOI: 10.1016/j.annonc.2021.08.2119]

34   **Yao JC**, Strosberg J, Fazio N, Pavel ME, Bergsland E, Ruszniewski P, Halperin DM, Li D, Tafuto S, Raj N, Campana D, Hijioka S, Raderer M, Guimbaud R, Gajate P, Pusceddu S, Reising A, Degtyarev E, Shilkrut M, Eddy S, Singh S. Spartalizumab in metastatic, well/poorly-differentiated neuroendocrine neoplasms. *Endocr Relat Cancer* 2021 [PMID: 33480358 DOI: 10.1530/ERC-20-0382]

35   **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]

36   **Al-Toubah T**, Halfdanarson T, Gile J, Morse B, Sommerer K, Strosberg J. Efficacy of ipilimumab and nivolumab in patients with high-grade neuroendocrine neoplasms. *ESMO Open* 2022; **7**: 100364 [PMID: 34973511 DOI: 10.1016/j.esmoop.2021.100364]

37   **Patel SP**, Othus M, Chae YK, Giles FJ, Hansel DE, Singh PP, Fontaine A, Shah MH, Kasi A, Baghdadi TA, Matrana M, Gatalica Z, Korn WM, Hayward J, McLeod C, Chen HX, Sharon E, Mayerson E, 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 1609) in Patients with Nonpancreatic Neuroendocrine Tumors. *Clin Cancer Res* 2020; **26**: 2290-2296 [PMID: 31969335 DOI: 10.1158/1078-0432.CCR-19-3356]

38   **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]

39   **Mohamed A**, Vijayvergia N, Kurian M, Liu L, Fu P, Das S. Exploring Real World Outcomes with Nivolumab Plus Ipilimumab in Patients with Metastatic Extra-Pulmonary Neuroendocrine Carcinoma (EP-NEC). *Cancers (Basel)* 2022; **14** [PMID: 35681675 DOI: 10.3390/cancers14112695]

40   **Capdevila J**, Teule A, López C, García-Carbonero R, Benavent M, Custodio A, Cubillo A, Alonso V, Gordoa TA, Carmona-Bayonas A, Crespo G, Blanco-Codesido M, Jimenez-Fonseca P, Viúdez A, Muñoa ALC, Sevilla I, Llanos M, Segura A, Hernando-Cubero J, Manzano JL. 1157O A multi-cohort phase II study of durvalumab plus tremelimumab for the treatment of patients (pts) with advanced neuroendocrine neoplasms (NENs) of gastroenteropancreatic or lung origin: The DUNE trial (GETNE 1601). *Ann Oncol* 2020; **31**: S770-S771 [DOI: 10.1016/j.annonc.2020.08.1370]

41   **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, Casta AL, 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: the phase II DUNE trial (GETNE 1601). In Review [DOI: 10.21203/rs.3.rs-2174016/v1]

42   **Shigeta K**, Datta M, Hato T, Kitahara S, Chen IX, Matsui A, Kikuchi H, Mamessier E, Aoki S, Ramjiawan RR, Ochiai H, Bardeesy N, Huang P, Cobbold M, Zhu AX, Jain RK, Duda DG. Dual Programmed Death Receptor-1 and Vascular Endothelial Growth Factor Receptor-2 Blockade Promotes Vascular Normalization and Enhances Antitumor Immune Responses in Hepatocellular Carcinoma. *Hepatology* 2020; **71**: 1247-1261 [PMID: 31378984 DOI: 10.1002/hep.30889]

43   **Yang J**, Yan J, Liu B. Targeting VEGF/VEGFR to Modulate Antitumor Immunity. *Front Immunol* 2018; **9**: 978 [PMID: 29774034 DOI: 10.3389/fimmu.2018.00978]

44   **Halperin DM**, Liu S, Dasari A, Fogelman DR, Bhosale P, Mahvash A, Dervin S, Estrella J, Cortazar P, Maru DM, Mckenna EF, Wistuba II, Schulze K, Futreal PA, Darbonne WC, Yun C, Hwu P, Yao JC. A phase II trial of atezolizumab and bevacizumab in patients with advanced, progressive neuroendocrine tumors (NETs). *JCO* 2020; **38**: 619-619 [DOI: 10.1200/JCO.2020.38.4_suppl.619]

45   **Halperin DM**, Liu S, Dasari A, Fogelman D, Bhosale P, Mahvash A, Estrella JS, Rubin L, Morani AC, Knafl M, Overeem TA, Fu S-C, Solis LM, Parra Cuentas E, Verma A, Chen H-L, 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 Oncology* 2022; **8**: 904-909 [DOI: 10.1001/jamaoncol.2022.0212]

46   **Al-Toubah T**, Morse B, Haider M, Valone T, Strosberg J. Phase II Study of Pembrolizumab and Lenvatinib in Advanced Well-Differentiated Neuroendocrine Tumors. *Endocrine Abstracts* 2023; **89** [DOI: 10.1530/endoabs.89.C8]

47   **Chan JA**, Raj NP, Aggarwal RR, Calabrese S, DeMore A, Dhawan MS, Fattah D, Fong L, Grabowsky J, Hope TA, Kolli KP, Munster PN, Perez K, Reidy DL, Von Fedak S, Zhang L, Bergsland EK. Phase II study of pembrolizumab-based therapy in previously treated extrapulmonary poorly differentiated neuroendocrine carcinomas: Results of Part B (pembrolizumab + chemotherapy). *JCO* 2021; **39**: 4148-4148 [DOI: 10.1200/JCO.2021.39.15_suppl.4148]

48   **Owen DH**, Wei L, Goyal A, Zhou Y, Suffren S-A, Jacob R, Pilcher C, Otterson GA, Verschraegen CF, Shah MH, Konda B. CLO20-054: A Phase 2 Trial of Nivolumab and Temozolomide in Advanced Neuroendocrine Tumors (NETs): Interim Efficacy Analysis. *J Natl Compr Canc Netw* 2020; **18**: CLO20-054 [DOI: 10.6004/jnccn.2019.7460]

49   **Riesco-Martinez MC**, Capdevila J, Alonso V, Jimenez-Fonseca P, Teule A, Grande E, Sevilla I, Viñuales MB, Alonso-Gordoa T, Custodio A, Hernando J, Polo E, Trujillo OAC, Garcia-Carbonero R. 1098O Nivolumab plus platinum-doublet chemotherapy as first-line therapy in unresectable, locally advanced or metastatic G3 neuroendocrine Neoplasms (NENs) of the gastroenteropancreatic (GEP) tract or unknown (UK) origin: Preliminary results from the phase II NICE-NEC trial (GETNE T1913). *Ann Oncol* 2021; **32**: S908-S909 [DOI: 10.1016/j.annonc.2021.08.180]

50   **Riesco Martinez MC**, Capdevila Castillon J, Alonso V, Jimenez-Fonseca P, Teule A, Grande E, Sevilla I, Benavent M, Alonso-Gordoa T, Custodio A, Antón Pascual B, Hernando J, Polo E, Castillo Trujillo OA, Garcia-Carbonero R. 496MO Final overall survival results from the

NICE-NEC trial (GETNE-T1913): A phase II study of nivolumab and platinum-doublet chemotherapy (CT) in untreated advanced G3 neuroendocrine neoplasms (NENs) of gastroenteropancreatic (GEP) or unknown (UK) origin. *Ann Oncol* 2022; **33**: S769 [DOI: 10.1016/j.annonc.2022.07.624]

51   **Chorath J**, Placencio-Hickok VR, Guan M, Nissen N, Kamrava M, Klempner SJ, Nassir Y, Hendifar A, Gong J. Durable Response to Carboplatin, Etoposide, Nivolumab, and Ipilimumab in Metastatic High-Grade Neuroendocrine Carcinoma of the Gallbladder. *Pancreas* 2020; **49**: e19-e20 [PMID: 32049953 DOI: 10.1097/MPA.0000000000001480]

52   **Galluzzi L**, Humeau J, Buqué A, Zitvogel L, Kroemer G. Immunostimulation with chemotherapy in the era of immune checkpoint inhibitors. *Nat Rev Clin Oncol* 2020; **17**: 725-741 [PMID: 32760014 DOI: 10.1038/s41571-020-0413-z]

53   **La Salvia A**, Barroso G, Espinosa Olarte P, Anton Pascual B, Modrego Sanchez A, Riesco-Martinez M, Garcia-Carbonero R.   High TMB and MSI-high as independent predictors of survival in NENs. In: Journal of Neuroendocrinology. WILEY 111 RIVER ST, HOBOKEN 07030-5774, NJ USA, 2021: 108-108

54   **Venizelos A**, Elvebakken H, Perren A, Nikolaienko O, Deng W, Lothe IMB, Couvelard A, Hjortland GO, Sundlöv A, Svensson J, Garresori H, Kersten C, Hofsli E, Detlefsen S, Krogh M, Sorbye H, Knappskog S. The molecular characteristics of high-grade gastroenteropancreatic neuroendocrine neoplasms. *Endocr Relat Cancer* 2021; **29**: 1-14 [PMID: 34647903 DOI: 10.1530/ERC-21-0152]

55   **Chalmers ZR**, Connelly CF, Fabrizio D, Gay L, Ali SM, Ennis R, Schrock A, Campbell B, Shlien A, Chmielecki J, Huang F, He Y, Sun J, Tabori U, Kennedy M, Lieber DS, Roels S, White J, Otto GA, Ross JS, Garraway L, Miller VA, Stephens PJ, Frampton GM. Analysis of 100,000 human cancer genomes reveals the landscape of tumor mutational burden. *Genome Med* 2017; **9**: 34 [PMID: 28420421 DOI: 10.1186/s13073-017-0424-2]

56   **Samstein RM**, Lee CH, Shoushtari AN, Hellmann MD, Shen R, Janjigian YY, Barron DA, Zehir A, Jordan EJ, Omuro A, Kaley TJ, Kendall SM, Motzer RJ, Hakimi AA, Voss MH, Russo P, Rosenberg J, Iyer G, Bochner BH, Bajorin DF, Al-Ahmadie HA, Chaft JE, Rudin CM, Riely GJ, Baxi S, Ho AL, Wong RJ, Pfister DG, Wolchok JD, Barker CA, Gutin PH, Brennan CW, Tabar V, Mellinghoff IK, DeAngelis LM, Ariyan CE, Lee N, Tap WD, Gounder MM, D'Angelo SP, Saltz L, Stadler ZK, Scher HI, Baselga J, Razavi P, Klebanoff CA, Yaeger R, Segal NH, Ku GY, DeMatteo RP, Ladanyi M, Rizvi NA, Berger MF, Riaz N, Solit DB, Chan TA, Morris LGT. Tumor mutational load predicts survival after immunotherapy across multiple cancer types. *Nat Genet* 2019; **51**: 202-206 [PMID: 30643254 DOI: 10.1038/s41588-018-0312-8]

57   **Cives M**, Pelle' E, Strosberg J. Emerging Treatment Options for Gastroenteropancreatic Neuroendocrine Tumors. *J Clin Med* 2020; **9** [PMID: 33202931 DOI: 10.3390/jcm9113655]

58   **Robinson MD**, Livesey D, Hubner RA, Valle JW, McNamara MG. Future therapeutic strategies in the treatment of extrapulmonary neuroendocrine carcinoma: a review. *Ther Adv Med Oncol* 2023; **15**: 17588359231156870 [PMID: 36872945 DOI: 10.1177/17588359231156870]

59   **Oberg K**, Modlin IM, De Herder W, Pavel M, Klimstra D, Frilling A, Metz DC, Heaney A, Kwekkeboom D, Strosberg J, Meyer T, Moss SF, Washington K, Wolin E, Liu E, Goldenring J. Consensus on biomarkers for neuroendocrine tumour disease. *Lancet Oncol* 2015; **16**: e435-e446 [PMID: 26370353 DOI: 10.1016/S1470-2045(15)00186-2]

60   **Malczewska A**, Oberg K, Kos-Kudla B. NETest is superior to chromogranin A in neuroendocrine neoplasia: a prospective ENETS CoE analysis. *Endocr Connect* 2021; **10**: 110-123 [PMID: 33289691 DOI: 10.1530/EC-20-0417]

61   **Woolaver RA**, Wang X, Krinsky AL, Waschke BC, Chen SMY, Popolizio V, Nicklawsky AG, Gao D, Chen Z, Jimeno A, Wang XJ, Wang JH. Differences in TCR repertoire and T cell activation underlie the divergent outcomes of antitumor immune responses in tumor-eradicating *vs* tumor-progressing hosts. *J Immunother Cancer* 2021; **9** [PMID: 33414263 DOI: 10.1136/jitc-2020-001615]

62   **Galon J**, Bruni D. Approaches to treat immune hot, altered and cold tumours with combination immunotherapies. *Nat Rev Drug Discov* 2019; **18**: 197-218 [PMID: 30610226 DOI: 10.1038/s41573-018-0007-y]

63   **Hegde PS**, Karanikas V, Evers S. The Where, the When, and the How of Immune Monitoring for Cancer Immunotherapies in the Era of Checkpoint Inhibition. *Clin Cancer Res* 2016; **22**: 1865-1874 [PMID: 27084740 DOI: 10.1158/1078-0432.CCR-15-1507]

64   **Takahashi D**, Kojima M, Suzuki T, Sugimoto M, Kobayashi S, Takahashi S, Konishi M, Gotohda N, Ikeda M, Nakatsura T, Ochiai A, Nagino M. Profiling the Tumour Immune Microenvironment in Pancreatic Neuroendocrine Neoplasms with Multispectral Imaging Indicates Distinct Subpopulation Characteristics Concordant with WHO 2017 Classification. *Sci Rep* 2018; **8**: 13166 [PMID: 30177687 DOI: 10.1038/s41598-018-31383-9]

65   **Bösch F**, Brüwer K, Altendorf-Hofmann A, Auernhammer CJ, Spitzweg C, Westphalen CB, Boeck S, Schubert-Fritschle G, Werner J, Heinemann V, Kirchner T, Angele M, Knösel T. Immune checkpoint markers in gastroenteropancreatic neuroendocrine neoplasia. *Endocr Relat Cancer* 2019; **26**: 293-301 [PMID: 30608901 DOI: 10.1530/ERC-18-0494]

66   **Pinato DJ**, Vallipuram A, Evans JS, Wong C, Zhang H, Brown M, Dina RE, Trivedi P, Akarca AU, Marafioti T, Mauri FA, Sharma R. Programmed Cell Death Ligand Expression Drives Immune Tolerogenesis across the Diverse Subtypes of Neuroendocrine Tumours. *Neuroendocrinology* 2021; **111**: 465-474 [PMID: 32097935 DOI: 10.1159/000506745]

67   **Cives M**, Strosberg J, Al Diffalha S, Coppola D. Analysis of the immune landscape of small bowel neuroendocrine tumors. *Endocr Relat Cancer* 2019; **26**: 119-130 [PMID: 30400003 DOI: 10.1530/ERC-18-0189]

68   **Young K**, Lawlor RT, Ragulan C, Patil Y, Mafficini A, Bersani S, Antonello D, Mansfield D, Cingarlini S, Landoni L, Pea A, Luchini C, Piredda L, Kannan N, Nyamundanda G, Morganstein D, Chau I, Wiedenmann B, Milella M, Melcher A, Cunningham D, Starling N, Scarpa A, Sadanandam A. Immune landscape, evolution, hypoxia-mediated viral mimicry pathways and therapeutic potential in molecular subtypes of pancreatic neuroendocrine tumours. *Gut* 2021; **70**: 1904-1913 [PMID: 32883872 DOI: 10.1136/gutjnl-2020-321016]

69   **Gubbi S**, Vijayvergia N, Yu JQ, Klubo-Gwiezdzinska J, Koch CA. Immune Checkpoint Inhibitor Therapy in Neuroendocrine Tumors. *Horm Metab Res* 2022; **54**: 795-812 [PMID: 35878617 DOI: 10.1055/a-1908-7790]

70   **Kubli SP**, Berger T, Araujo DV, Siu LL, Mak TW. Beyond immune checkpoint blockade: emerging immunological strategies. *Nat Rev Drug Discov* 2021; **20**: 899-919 [PMID: 33686237 DOI: 10.1038/s41573-021-00155-y]