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**Progress in immunotherapy for neuroendocrine neoplasm of the digestive system**

Pan WX *et al*. Immunotherapy for the digestive system's NEN

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**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

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**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 hepatopancreatobiliary 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 mm2. 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 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 spartalizumab 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, 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.

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**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.

**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 + Tislelizumab | 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 + Pembrolizumab | 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.



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