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MINIREVIEWS

Immunotherapies for well-differentiated grade 3 gastroenteropancreatic neuroendocrine tumors: A new category in the World Health Organization classification

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Abstract

According to the 2019 World Health Organization (WHO) classification, well-differentiated grade 3 (G3) gastroenteropancreatic (GEP) neuroendocrine tumors (NETs) are a new category of cancer of the digestive system. G3 GEP-NET research and treatment are not as robust as those of lower grade (G1/2) NETs and poorly differentiated neuroendocrine carcinomas (NECs). Previously, the management of high-grade NETs was mainly based on NEC therapies, as high-grade NETs were classified as NECs under the previous WHO classification. Despite this, G3 GEP-NETs are significantly less responsive to platinum-based chemotherapy regimens than NECs, due to their distinct molecular pathogenesis and course of pathological grade transition. Patients with advanced G3 GEP-NETs, who have progressed or are intolerant to chemotherapy regimens such as capecitabine plus temozolomide, have limited treatment choices. Immunotherapy has helped patients with a variety of cancers attain long-term survival through the use of immune checkpoint inhibitors. Immunotherapies, either alone or in combination with other therapies, do not have a clear function in the treatment of G3 GEP-NETs. Currently, the majority of immunotherapy studies, both prospective and retrospective, do not reliably differentiate G3 GEP-NETs from NECs. By contrast, a significant number of studies include non-GEP neuroendocrine neoplasms (NENs). Therefore, there is an urgent need to summarize and evaluate these data to provide more effective therapeutic approaches for patients with this rare tumor. The purpose of this mini-review was to screen and

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summarize information on G3 GEP-NETs from all studies on NENs immunotherapy.

Key Words: Gastrointestinal tract; Pancreas; Immune checkpoint inhibitors; Immunotherapy; Neuroendocrine tumors; Cytotoxic T-lymphocyte-associated protein 4 antigen

Core Tip: Several evaluations have been published on immunotherapy for neuroendocrine neoplasms. However, this is the first review to specifically focus on the efficacy of different immunotherapy strategies such as immune checkpoint inhibitor (ICI) monotherapy, dual ICI therapy, anti-angiogenesis plus ICI, and chemotherapy combined with ICI for the treatment of advanced well-differentiated high-grade gastroenteropancreatic neuroendocrine tumors.

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INTRODUCTION

Neuroendocrine neoplasms (NENs) are rare and indolent diseases that can manifest in any part of the body where peptidergic neurons and neuroendocrine cells are found. About 65% of neoplasms are found in the gastrointestinal (GI) tract and pancreas, making gastroenteropancreatic (GEP)-NENs the most common type of NENs[1]. Due to advancements in early-stage disease detection techniques such as endoscopy and imaging, the incidence of GEP-NENs has significantly increased to an overall incidence of 3.56 per 100000[2]. Based on the 2010 grading system, the World Health Organization (WHO) in 2019 comprehensively considered the importance of the primary site, morphological differentiation, and grading in the classification of GEP-NENs, and expanded the 2017 grading system by proposing a classification framework for all NENs[3]. One of the key updates in the 2019 classification system is that all grade 3 (G3) NENs (with Ki-67 proliferation index > 20%) are classified as either well-differentiated G3 neuroendocrine tumors (NETs) or poorly differentiated neuroendocrine carcinomas (NECs). Although G3 NETs have more inert biological behavior compared to NECs, they have a poorer prognosis compared to G1/2 NETs [4]. Compared to patients with poorly differentiated NECs, well-differentiated G3 NET patients have a considerably longer median overall survival (mOS) (41-99 mo *vs* 17 mo)[5].

G3 NENs account for 13.4% of all digestive system NENs, whereas G3 NETs account for 18%-20% of G3 GEP-NENs[6,7]. In general, although significant progress has been made in the management of GEP-NENs as a whole, the treatment of G3 GEP-NETs, a new WHO category, has not been well studied. Therefore, more tailored treatment strategies are needed for these disorders.

According to WHO 2010 classification criteria, G3 GEP-NETs were categorized as NECs. However, clinical variations between individuals with G3 GEP-NETs and NECs were discovered. For example, platinum-based chemotherapy was frequently employed for the treatment of G3 GEP-NEN patients in the past. Patients with G3 NETs or Ki-67 < 55% (mostly well-differentiated) were significantly less responsive to treatment than those with NEC or Ki-67 ≥ 55% (mostly poorly differentiated). G3 NET and NEC patients have an objective response rate (ORR) of less than 17% and 35%-70%, a median progression-free survival rate (mPFS) of 2.4-4 mo and 5.0 mo, and mOS of 17 mo and 99 mo, respectively[8-10].

Recently, the first prospective Phase II study of capecitabine with temozolomide in patients with high-grade GEP-NEN and Ki-67 index < 55% yielded results contrary to those received platinum plus etoposide. Patients with G3 NET (n = 23) responded better to treatment than those with NEC (n = 7) in both short-term [ORR 34.8% *vs*

14.3%, P = 0.393; disease control rate (DCR) 87.0% *vs* 42.9%, P = 0.033] and long-term (mPFS 9.3 mo *vs* 3.5 mo, P = 0.005; mOS did not reach *vs* 6.2 mo, P = 0.004) evaluations [11]. In addition, a retrospective study showed that the first-line fluoropyrimidine-based regimens with oxaliplatin (FOLFOX/XELOX) also achieved superior results (mPFS of 7.9 mo and mOS of 30 mo) in 34 patients with G3 GEP-NETs[12].

However, there is no established treatment for G3 GEP-NET patients who are insensitive or resistant to chemotherapy. Peptide receptor radionuclide therapy (PRRT) is a promising alternative approach to chemotherapy. In a retrospective cohort study, PRRT was delivered to G3 GEP NEN patients and their response was examined. The study found that ORR was not significantly different across well-differentiated (n = 60) and poorly differentiated (n = 62) disease subgroups (42% *vs* 43%). However, DCR, mPFS, and mOS were much longer in patients with well-differentiated tumors than those with poorly differentiated cancers (DCR 93% *vs* 68%, mPFS 19 mo *vs* 8 mo, and mOS 44 mo *vs* 19 mo)[13]. Regrettably, this new therapy is only available in a few countries. Therefore, there is an urgent need to compensate for the inadequacies of the aforementioned medications in patients with G3 GEP-NETs.

In recent years, immunotherapy has emerged as a new and intriguing approach for cancer therapy. Cancer cells have the inherent ability to express negative regulatory molecules of immune cells. The cornerstone of immunotherapy in modern oncology aims to improve the ability of the immune system to recognize and kill tumor cells [14]. Currently, this is being achieved through the use of monoclonal antibodies against immune checkpoints such as programmed death-ligand 1 (PD-L1)/programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). Immune checkpoint inhibitors (ICIs), which sit at the forefront of cancer immunotherapy, have revolutionized the management of a variety of solid malignancies. In relation to NENs, immunotherapy has been mainly used to treat lung and skin tumors such as Merkel cell carcinoma, malignant melanoma, and small cell lung cancer (SCLC)[15]. Although an increasing number of clinical trials and retrospective studies are being conducted to investigate the efficacy of ICIs on NENs of the digestive tract, the role of immunotherapy approaches in well-differentiated G3 NETs has not been sufficiently studied.

In this minireview, we briefly describe the overall pathological changes of G3 GEP-NETs and analyze in detail the immunotherapy experience with well-differentiated G3 GEP-NETs from complex investigations.

ROLE OF IMMUNOTHERAPY IN G3 GEP-NETS

A recent systematic review and meta-analysis of 636 NEN patients treated with ICIs reported an ORR of 10% [95% confidence interval (CI): 6%-15%, I^2 = 67%, P < 0.1], a total DCR of 42%, a mPFS of 4.1 mo (95%CI: 2.6-5.4; I^2 = 96%, P < 0.1), and a mOS of 11 mo (95%CI: 4.8-21.1; I^2 = 98%, P < 0.1)[16]. This demonstrated the overall effectiveness of ICIs in treating NEN patients. Among the NEN study subjects, about 37% were patients with NENs originating from the lung or other unknown sites and only 13.4% were patients who had G3 NETs. However, the study did not include a separate subgroup of G3 GEP-NET patients in its analysis. Previous studies have shown that G3 NETs can share a common pathogenesis with G1-2 NETs[17]. Moreover, more than half of G1-2 pancreatic NETs (pNETs) developed progressively into G3 pNENs over time[18]. Some researchers have even speculated that high-grade pNET may develop from the initial low- and medium-grade NET, while pNEC may develop from pancreatic ductal adenocarcinoma[19,20]. Therefore, the response of lower grade NETs to immunotherapy may have some implications for the treatment of G3 NETs. Other aspects that may influence the immunotherapy choices for G3 GEP-NETs include the presence of predictive biomarkers for ICIs in tumors with high proliferative activity as well as changes in pathological grade over time.

Table 1 summarizes the clinical trials of immunotherapy in GEP-NENs. Below, we presented data from clinical trials and retrospective studies that may have included cases with G3 GEP-NETs. Additionally, we analyzed the data to determine the efficacy of different immunotherapy strategies such as PD-1/PD-L1 inhibitors as a monotherapy or in combination with CTLA-4 inhibitors, anti-angiogenesis, and chemotherapy in the management of these rare diseases.

ICIs monotherapy

Pembrolizumab is the most extensively investigated immunotherapy for NENs. For example, phase Ib (KEYNOTE-28) and phase II (KEYNOTE-158) clinical trials were

Table 1 Clinical trials related to gastroenteropancreatic neuroendocrine tumors

ClinicalTrials.gov identifier	Intervention	Study phase	Trial name	Primary outcome	Estimated/actual enrollment, *n*	Estimated/actual date	Trial status	Medical condition related to advanced NENs	Reported assessable n of NENs
NCT02054806[21]	Pembrolizumab	Ib	Phase Ib study of pembrolizumab (MK-3475) in subjects with select advanced solid tumors (MK-3475-028/KEYNOTE-028)	ORR	477	April 30, 2021	Completed	pNETs: PD-L1 (+), well or moderately differentiated	16 pNETs
NCT02628067[22]	Pembrolizumab	II	A clinical trial of pembrolizumab (MK-3475) evaluating predictive biomarkers in subjects with advanced solid tumors (KEYNOTE-158)	ORR	1595	June 18, 2026	Recruiting	NETs: Well or moderately differentiated	107 NETs: Lung, appendix, small intestine, colon, rectum, or pan origin
NCT02939651[23]	Pembrolizumab	II	A phase 2, open-label study of pembrolizumab monotherapy in patients with metastatic high grade neuroendocrine tumors	ORR	21	March 2020	Completed	G3 NENs: Ki-67 > 20%, poorly or well-differentiated, failed for platinum based chemotherapy, excluding MCC, large/small cell NENs of lung/thymus origin	29 G3 NENs: 19 NECs, 9 G3 NET, 14 Ki-67 ≤ 50%, 12 Ki-67 > 50%, 10 pan, 14 GI, 5 unknown origin
NCT03136055[24, 48]	Part A: pembrolizumab alone; Part B: Pembrolizumab + chemotherapy	II	A pilot study of pembrolizumab-based therapy in previously treated high grade neuroendocrine carcinomas	ORR	36	May 31, 2023	Active, not recruiting	EP-PDNECs: Failed for first-line systemic therapy, excluding MCC or well differentiated G3 NET	Part A: 13 EP-PDNECs; Part B: 22 EP-PDNEC
NCT03190213	Pembrolizumab	II	Pembrolizumab for the treatment of recurrent high grade neuroendocrine carcinoma (Pembro NEC)	ORR (irRECIST)	6	March 11, 2019	Terminated	G3 NENs: Failed for platinum-based regimen or temozolomide-based regimen. exluding lung origin	6 G3 NENs
NCT02955069[25]	Spartalizumab	II	An open label phase II study to evaluate the efficacy and safety of PDR001 in patients with advanced or metastatic, well-differentiated, non-functional neuroendocrine tumors of pancreatic, gastrointestinal (GI), or thoracic origin or poorly-differentiated gastroenteropancreatic neuroendocrine carcinoma (GEP-NEC), that have progressed on prior treatment	ORR	116	May 13, 2020	Completed	NENs: Exclude G3 NETs and include G1/2 NET (non-functional, GEP or thoracic origin, failed to prior treatment) and GEP-NEC (progressed on or after one prior chemotherapy regimen)	99 NETs: 30 thoracic, 32 GI-NET, 33 pNET; 21 GEP-NEC
NCT03167853[30]	Toripalimab	Ib	Phase Ib study of safety and efficacy of recombinant humanized anti-PD-1 monoclonal antibody for patients with advanced neuroendocrine tumors following failure of first-line	ORR	40	May 11, 2019	Completed	NENs: Ki-67 ≥ 10%, nonfunctional NENs, well- or poorly-differentiated, failed for first line therapy	40 NENs: 8 well-differentiated, 32 poorly-differentiated
NCT03352934[26]	Avelumab	II	A phase II, open-label, multicenter trial to	DCR	60	January 2024	Active, not	G3 NENs: after first-line	29 G3 NENs: 16 NEC

			investigate the clinical activity and safety of avelumab in patients with advanced, metastatic high grade neuroendocrine carcinomas NEC G3 (WHO 2010) progressive after chemotherapy (AveNEC)				recruiting	chemotherapy, excluding MCC, SCLC	and 11 G3 NETs, 12 pan, 5 GI, 9 other origin)
NCT03278405[58]	Avelumab	IIa	A pilot study of avelumab in unresectable/metastatic, progressive, poorly differentiated grade 3 neuroendocrine carcinomas (NET001)	ORR	10	March 12, 2020	Completed	NECs: Poorly-differentiated, GI or lung origin, have received 0-2 prior lines of systemic therapy, excluding MANEC	10 NECs: 9 GI and 1 lung
NCT03278379[28]	Avelumab	II	A phase II study of avelumab in unresectable/metastatic, progressive grade 2-3 neuroendocrine tumors (NET-002)	ORR	17	September 20, 2021	Active, not recruiting	G2-3 NETs: GEP or lung, received 0-2 prior lines of therapy (excluding SSAs), excluding G1 NET, NEC and MANEC	17 G2-3 NETs (12 GEP, 5 lung)
NCT03147404	Avelumab	II	Phase II study of avelumab in metastatic gastronetro-pancreatic (GEP) neuroendocrine carcinoma (NEC, WHO Grade 3) as second-line treatment after failing to etoposide + cisplatin: integration of genomic analysis to identify predictive molecular subtypes (MS100070-0177)	Best response	14	July 22, 2019	Completed	G3 GEP-NECs: Second-line treatment after failing to etoposide + cisplatin	-
NCT03879057[39]	Toripalimab + surufatinib	I	Phase I trial evaluating the safety, tolerability, pharmacokinetics, and efficacy of surufatinib combined with JS001 in patients with advanced solid tumors	AEs, MTD	24	December 20, 2021	Recruiting	NENs: G1-3 NET, NEC	18 NENs:11 NECs,4 G2 NETs; 4 G3 NETs, 12 GI,4 pan, 1 lung
NCT04169672[40]	Toripalimab + surufatinib	II	A phase II, open-label, single-arm, multi-center study of the efficacy and safety of surufatinib combined with toripalimab in patients with advanced solid tumors	AEs, ORR	200	February 28, 2022	Recruiting	NECs: Refractory to first-line chemotherapy	20 NECs
NCT03475953	Avelumab + regorafenib	I/II	A phase I/II study of regorafenib plus avelumab in solid tumors (REGOMUNE)	Phase I: Recommended dose of regorafenib; Phase II: ORR, PFS	482	May 2022	Recruiting	G2/3 GEP-NETs	-
NCT03290079	Pembrolizumab + lenvatinib	II	Phase II study of pembrolizumab and lenvatinib in advanced well-differentiated neuroendocrine tumors	ORR	35	December 2023	Recruiting	NETs: Well-differentiated, lung, thymus, small bowel or colon origin, including unknown primary, excluding pNENs and poorly differentiated NECs	-
NCT04579757	Surufatinib + tislelizumab	Ib/II	An open-label phase Ib/II study of	DLT, ORR	120	April 30, 2023	Recruiting	G1/2 NETs: Thoracic or	-

			surufatinib in combination with tislelizumab in subjects with advanced solid tumors					GEP origins, have progressed on at least one line of standard therapy	
NCT04207463	AK105 + anlotinib	II	A phase II, open, single-arm, multi-cohort, multicenter study of anlotinib and AK105 (anti-PD-1) injection in subjects with gastrointestinal tumors, urinary system tumors, neuroendocrine tumors	ORR	150	May 30, 2021	Recruiting	G1/2 GEP-NETs	-
NCT03074513[41]	Atezolizumab + bevacizumab	II	A phase II, single-arm open-label study of the combination of atezolizumab and bevacizumab in rare solid tumors	ORR	164	March 31, 2021	Active, not recruiting	G1/2 NETs: pNET cohort and epNET cohort containing typical or atypical carcinoid if originating in lung	20 G1/2 pNETs, 20 G1/2 epNETs
NCT02923934[45]	Nivolumab + ipilimumab	II	A phase II clinical trial evaluating ipilimumab and nivolumab in combination for the treatment of rare gastrointestinal, neuro-endocrine and gynaecological cancers (CA209-538)	CBR	120	December 2023	Active, not recruiting	NENs: G1-3 NETs, NECs, GEP or lung origin	10 GEP-NENs: 7 pNENs (3 G3 pNETs, 2 pNECs, 2 G2 pNETs); 3 GI-NENs (1 gastro-oesophageal junction NEC, 1 colonic NECs, 1 G1 gastric NET)
NCT02834013[15, 46]	Nivolumab + ipilimumab	II	A prospective, open-label, multicenter phase II basket clinical trial of ipilimumab plus nivolumab across multiple rare tumor cohorts (DART)	ORR	818	August 1, 2021	Recruiting	SWOG 1609 cohort: Refractory epNENs. G3 NETs were included in G3 NECs. SWOG S1609 cohort: Dedicated cohort include G3 NENs	SWOG 1609 cohort: 32 epNENs (18 G3, 10 G2, 4 G1, 15 GI, 6 Lung). S1609 cohort: 19 G3 NENs (2 G3 NETs, 11 NEC, 6 unknown differentiation status)
NCT04969887	Nivolumab + ipilimumab	II	Ipilimumab and nivolumab combination therapy in patients with selected immunotherapy sensitive advanced rare cancers (MOST-CIRCUIT)	CBR	240	December 2024	Not yet recruiting	NECs and G3 NETs independent of primary site, excluding SCLC	-
NCT03591731	Nivolumab alone or nivolumab + ipilimumab	II	A GCO trial exploring the efficacy and safety of nivolumab monotherapy or nivolumab plus ipilimumab in pre-treated patients with advanced, refractory pulmonary or gastroenteropancreatic poorly differentiated neuroendocrine tumors (NECs) (NIPINEC)	ORR	180	September 2023	Recruiting	NECs: Poorly differentiated, refractory, pulmonary or GEP, excluding SCLC	-
NCT03095274[47]	Tremelimumab + durvalumab	II	A phase II study of durvalumab (MEDI4736) plus tremelimumab for the treatment of patients with advanced neuroendocrine neoplasms of gastroenteropancreatic or lung origin (DUNE) (GETNE 1601)	Cohort 1-3: CBR at 9 m; Cohort 4: OS at 9 mo	126	July 2021	Recruiting	G1/G2 NETs of GEP and lung, and G3 of GEP or unknown primary site (excluding lung primaries) after progression to standard therapies	123 NENs (Cohort 1: 27 typical/atypical lung carcinoid; Cohort 2: 31 G1/2 GI-NENs; Cohort 3: 32 G1/2 pNENs; Cohort 4: 33 G3 NEN of GEP or unknown primary site)

NCT04079712	Nivolumab + ipilimumab + cabozantinib	II	A phase 2 study of XL184 (Cabozantinib) in combination with nivolumab and ipilimumab for the treatment of poorly differentiated neuroendocrine carcinomas	ORR	30	October 1, 2021	Recruiting	NECs: All variations of poorly differentiated NECs (small cell, large cell and mixed cells) are eligible, excluding SCLC and MCC. Failure of only one line of prior systemic cancer treatment	-
NCT03728361[49]	Nivolumab + temozolomide	II	A phase II, multi-cohort trial of combination nivolumab and temozolomide in recurrent/refractory small-cell lung cancer and advanced neuroendocrine tumors	ORR	55	December 31, 2021	Active, not recruiting	NENs: Any grade or primary site	12 NENs: 1 G1, 8 G2, 3 G3
NCT03980925	Nivolumab + platinum-doublet chemotherapy	II	A phase II study of platinum-doublet chemotherapy in combination with nivolumab as first-line treatment in subjects with unresectable, locally advanced or metastatic G3 neuroendocrine neoplasms (NENs) of the gastroenteropancreatic (GEP) tract or of unknown (UK) origin (GETNE-T1913)	OS at 12 mo	38	December 2022	Recruiting	G3 NENs: GEP or unknown primary site	-
NCT03365791[59]	Spartalizumab + LAG525	II	Modular phase 2 study to link combination immune-therapy to patients with advanced solid and hematologic malignancies. Module 9: PDR001 plus LAG525 for patients with advanced solid and hematologic malignancies	CBR at 24 wk	76	September 17, 2020	Completed	NETs: Well-differentiated, relapsed and/or refractory to available standard of care therapies	7 NETs
NCT03043664[60]	Pembrolizumab + lanreotide depot	Ib/II	Phase Ib/II study of pembrolizumab with lanreotide depot for gastroenteropancreatic neuroendocrine tumors (PLANET)	ORR	22	September 1, 2021	Active, not recruiting	G1-2 GEP-NETs: Had progressed on a prior SSA	22 G1/2 GEP-NETs (14 GI, 8 pan)
NCT04525638	Nivolumab + ^{177}Lu-DOTATATE	II	A phase II single arm trial evaluating the preliminary efficacy of the combination of ^{177}Lu-DOTATATE and nivolumab in grade 3 well-differentiated neuroendocrine tumours (NET) or poorly differentiated neuroendocrine carcinomas (NEC)	ORR	30	September 30, 2024	Recruiting	G3 NENs: GEP or unknown primary site, well-differentiated or poorly-differentiated.	-
NCT04701307	Dostarlimab + niraparib	II	Niraparib (PARP Inhibitor) plus dostarlimab (Anti-PD1) for small cell lung cancer (SCLC) and other high-grade neuroendocrine carcinomas (NEC)	6 mo PFS, 3 mo ORR	48	May 30, 2025	Recruiting	G3 NECs: SCLC (Cohort 1) and other G3 NECs (Cohort 2), had at least one prior line of systemic therapy, excluding prostate origin	-
NCT03457948	Group I: Pembrolizumab + ^{177}Lu DOTATATE; Group II: Pembrolizumab + TAE; Group III: Pembrolizumab + ^{90}Yttrium- Microsphere Radioembolization	II	A pilot study of pembrolizumab and liver-directed therapy or peptide receptor radionuclide therapy for patients with well-differentiated neuroendocrine tumors and symptomatic and/or progressive metastases	ORR	32	March 31, 2024	Recruiting	G1-3 NETs: Well-differentiated, any primary site and unknown primary site, have liver metastases	-

NCT03879694	SVN53-67/M57-KLH peptide vaccine (SurVaxM) +Octreotide	I	A phase I study of safety and immunogenicity of Survivin Long Peptide Vaccine (SurVaxM) in patients with metastatic neuroendocrine tumors (NETs)	AEs	10	June 13, 2024	Recruiting	NETs: GEP or lung origin, positive for survivin	-
NCT04166006	Dendritic cells loaded with autologous tumour (DC vaccine) + IL-2	II	A phase II study on adjuvant vaccination with dendritic cells loaded with autologous tumor homogenate in resected stage iv rare cancers: Head & neck (H & N), neuroendocrine tumors (NET) and soft tissue sarcoma (STS)	Treatment-Emergent AEs	51	December 2026	Recruiting	NET: Stage IV	-

AE: Adverse event; CBR: Clinical benefit rate; DCR: Disease control rate; DLT: Dose-limiting toxicity; EP-PDNECs: Extrapulmonary poorly differentiated neuroendocrine carcinomas; ep: Extra-pancreatic; G1, 2, 3: Grade 1, 2, 3; GEP: Gastroenteropancreatic; GI: Gastrointestinal; irRECIST: Immune-related Response Evaluation Criteria in Solid Tumors; MANEC: Mixed adenoneuroendocrine carcinomas; MCC: Merkel cell carcinoma; MTD: Maximum tolerated dose; NECs: Neuroendocrine carcinomas; NENs: Neuroendocrine neoplasms; NETs: Neuroendocrine tumors; ORR: Objective response rate; OS: Overall survival; p: Pancreatic; pan: Pancreas origin; PD-1: Programmed cell death protein 1; PD-L1: Programmed death-ligand 1; PFS: Progression-free survival; SCLC: Small cell lung cancer; WHO: World Health Organization.

conducted to evaluate pembrolizumab monotherapy in patients with moderately or well-differentiated NETs. In these two studies, no data on tumor grade and Ki-67 index were collected. The results of the KEYNOTE-28 trial showed an ORR of 6.3% in pNETs[21]. The preliminary results of the KEYNOTE-158 study showed that mixed NETs had an ORR of 3.7% and that all reactive tumors were PD-L1-negative[22]. In addition, two prospective randomized phase II trials were performed to evaluate pembrolizumab in 19 patients with NECs and 9 with G3 NETs. There were no responses to pembrolizumab in patients with GI tract or pancreatic diseases[23]. In a trial of 14 patients with extrapulmonary poorly differentiated NECs, only 1 patient achieved complete remission (CR) (ORR 7%) following pembrolizumab monotherapy [24]. From the abovementioned studies, it can be concluded that pembrolizumab alone has a very limited curative effect on the GEP-NENs independent of their proliferative activity or differentiation. The only clinical trial (NCT02955069) of spartalizumab, a PD-1 inhibitor, for the treatment of NENs excluded patients with G3 NETs and achieved low efficacy comparable to pembrolizumab[25]. Avelumab is the only PD-L1 inhibitor used as a single drug in prospective clinical trials for GEP-NENs. Four phase II clinical trials (NCT03352934[26], NCT03278405[27], NCT03278379[28], and NCT03147404) were conducted to evaluate avelumab in patients with G2/3 NETs or NEC. The trials revealed that none of the patients achieved an objective response to avelumab treatment. In addition, none of the 3 G3 NET patients analyzed in a retrospective study from the Mayo Clinic exhibited an objective response to ICI (pembrolizumab, nivolumab, or atezolizumab) monotherapy[29].

Toripalimab (JS001) is a humanized PD-1 IgG4 monoclonal antibody developed in China. In a phase Ib study (NCT03167853) involving 40 NEN patients with Ki-67 ≥ 10%, toripalimab showed moderate efficacy in both well-differentiated NETs and poorly differentiated NECs (ORR: 25.0% *vs* 18.7% per RECIST 1.1, 25.0% *vs* 25.0% per irRECIST)[30]. This suggests that toripalimab may be the most effective ICI

monotherapy currently available for NENs, including G3 NETs. The study also found that patients with PD-L1 expression ≥ 10% or with high tumor mutational burden (TMB) had a better ORR than patients with PD-L1 < 10% (50.0% *vs* 10.7%, $P = 0.019$) or with low TMB (75.0% *vs* 16.1%, $P = 0.03$)[30].

Anti-angiogenesis combined with ICIs

NENs from different tissues are highly vascularized and express a variety of growth factors including vascular endothelial growth factor (VEGF), platelet-derived growth factor, basic fibroblast growth factor, insulin-like growth factor 1, and transforming growth factor-α/β[31]. The high exposure and activation of VEGFs prevent the immune system from recognizing and killing cancer cells killing tumor cells[32,33].

The hallmark of angiogenesis is the uncontrolled development of new vessels from adjacent normal tissues. This results in a network of immature microvessels characterized by structural and functional abnormalities. The normalizing vascular structure can be achieved with antiangiogenic drugs, including large-molecule monoclonal antibodies and small-molecule tyrosine kinase inhibitors. This results in the activation of adhesion molecules and chemokines that recruit and attract cytotoxic T cells and reduce the entry of regulatory T cells. Moreover, it contributes to immune cell mobilization[34,35].

Surufatinib is a small molecule inhibitor that mainly targets VEGF-1, 2, 3 (VEGFR-1, 2, 3), fibroblast growth factor receptor-1, and colony-stimulating factor-1 receptor (CSF-1R). Blocking of CSF-1R can reduce the polarization of tumor-associated macrophages to the M2 type that participates in immunosuppression and promotes tumor growth[36,37]. Two randomized, double-blind phase III clinical trials (SANET-ep and SANET-p) were carried out to evaluate surufatinib *vs* placebo in Chinese patients with G1-2 NETs. The results indicated that surufatinib can significantly prolong PFS in patients with advanced pancreatic and non-pancreatic G1-2 NETs compared with placebo[37,38]. At present, a phase I trial and a phase II trial of surufatinib combined with toripalimab on patients with NENs are underway. In a phase I clinical trial (NCT03879057), as of 2020-1-20, PR occurred in G1/2 NET (2/4) and NECs (2/11) patients; however, none of the 4 patients with G3 NETs achieved disease remission[39], which may be attributed to the small sample size of patients with G3NETs. In the phase II trial (NCT04169672), 20 evaluable patients with NECs and refractory to first-line chemotherapy achieved a moderate ORR of 20% and a DCR of 70%[40]. However, no data for well-differentiated NETs have been reported. In addition, two prospective studies involving G3 GEP-NETs patients are currently recruiting. In one of the trials, the intervention is avelumab plus regorafenib, while in the other study, the intervention is pembrolizumab plus lenvatinib. The studies are expected to be completed in May 2022 and December 2023, respectively. The combination treatment of atezolizumab and bevacizumab in a phase II basket trial (NCT03074513) showed moderate clinical activity and good tolerance in G1-2 pNETs and extra-pNETs (ORR 20% and 15%, respectively) patients with prior therapy[41]. However, the data of G3 NETs have not been reported either.

Given the favorable preliminary results in patients with G1-2 NETs and NECs, researchers might be optimistic about the combination therapy's effectiveness in patients with G3 NETs.

Dual ICI therapy

The United States Food and Drug Administration has approved ipilimumab (anti-CTLA-4) combined with nivolumab (anti-PD-1) (N+I) for melanoma, metastatic renal cell carcinoma, advanced hepatocellular carcinoma, and previously untreated unresectable malignant pleural mesothelioma[42-44]. Response rates with this combination are higher compared to single-agent anti-PD-1 therapy. For NENs, a phase II clinical trial (CA209-538) of N+I demonstrated a moderate overall ORR of 24%, especially in patients with G3 NENs and atypical bronchial carcinoid[45]. In the study, 7 patients with pNENs and 3 with GI-NENs achieved an ORR of 43% and 33.3%, respectively. All responders had a high-grade disease. It is worth noting that 2 of the 3 patients with G3 pNET achieved an objective response. This result is a breakthrough in the application of ICIs in the treatment of G3 GEP-NET. Currently, a phase II study (NCT04969887) on evaluation of N+I in patients with immunotherapy-sensitive cancers including NECs and G3 NETs from CA209-538 has been registered and is expected to be completed in October 2024.

Another phase II basket study of N+I for the treatment of rare tumors called SWOG DART (NCT02834013) was recently reported. In one cohort, 32 patients with epNENs (excluding SCLC, about 50% have GI-NENs) had a significantly higher response rate for high-grade neoplasms than for middle/low-grade neoplasms (ORR 44% *vs* 0%, $P =$

0.004) with no difference in overall ORR between the different primary origins[15]. Based on the results of the cohort, a second and dedicated cohort of 19 individuals with G3 NENs was explored[46]. Although all patients were microsatellite-stable, the results of the cohort revealed a moderate ORR of 26%. Unfortunately, none of the above cohorts performed an analysis of G3 NENs according to differentiation. A similar dilemma existed in a retrospective study at Moffet Cancer Center and the Mayo Clinic, where G3 NEN patients achieved an ORR of 14.75%. Therefore, determining the efficacy of N+I in the treatment of well-differentiated G3 GEP-NETs is challenging.

Durvalumab (anti-PD-L1) in combination with tremelimumab (anti-CTLA-4) (D+T) is another dual ICI therapy that has been studied for advanced NENs of GEP or lung origin. The initial results of DUNE, a prospective phase II multi-cohort study, were presented at the 2020 ESMO Annual meeting[47]. Cohort 4 consisting of 33 G3 GEP-NENs achieved an ORR of 9.1%, and the clinical benefit rate of 36.1% at 9-mo paved the way for a phase III clinical trial of D+T. Regrettably, comparable to N+I, no independent examination of patients with well-differentiated tumors was conducted, although the efficacy of G3 was higher than that of G1-2.

The above results suggest that dual ICIs have moderate overall efficacy in patients with advanced G3 GEP-NENs. Comparatively, the N+I regimen appears to have a greater response rate than D+T. The success of these therapies, however, must be demonstrated in a large number of patients with well-differentiated G3 GEP-NETs.

Chemotherapy combined with ICI

Current research on chemotherapy combined with ICIs, in the field of GEP-NENs, has a small sample size and the majority of them include previously treated NECs. The ORRs vary from 9% for pembrolizumab plus dealers' choice chemotherapy to 36% for nivolumab plus temozolomide[29,48,49]. Since most NEC patients are sensitive to chemotherapy, it is necessary to compare the above results with the data of chemotherapy alone as a second- or later-line treatment option. This comparison will establish whether NEC patients can significantly benefit from the above combination therapy. As previously described, G3 NETs are insensitive to platinum-based chemotherapy. Unfortunately, G3 GEP-NET, as a well-differentiated tumor with high proliferative activity, has not been specifically included in any prospective clinical trials for chemotherapy combined with ICI.

Other immunotherapies

Immunotherapies currently being investigated in prospective clinical trials related to G3 GEP-NET include classic PD-1 inhibitors combined with other therapies such as LAG525 (LAG-3 inhibitor), ^{177}Lu-DOTATATE (PRRT), and liver-directed therapies (Transarterial Embolization or ^{90}Yttrium Microsphere Radioembolization). In addition, the immune tumor vaccines Survivin Long Peptide Vaccine (SurVaxM) and Dendritic Cells Loaded with Autologous Tumor Homogenate (DC vaccine) have entered phase I and phase II clinical trials, respectively. Both vaccines are currently at the subject recruitment stage.

Predictive biomarkers for immunotherapies

The potential of a given patient with G3 GEP-NET to respond to immunotherapies is still largely unknown. NETs can be considered as immunologically "cold" due to their lack of immunoactive cellular components, low tumor antigens, *etc*.[50,51].

Immunohistochemical assessment of PD-L1 expression and its role in predicting response to ICIs is an incredibly hot topic. However, in the KEYNOTE-28 study, pNETs with positive PD-L1 expression achieved a low ORR of 6.3%[21]. In the KEYNOTE-158 study, all 4 GEP-NET patients who achieved PR had negative PD-L1 expression[22]. Besides, in a joint analysis of two prospective, non-randomized trials, no difference in DCR, PFS, or OS was observed between the PD-L1-negative and PD-L1-positive groups with G3 NENs[23]. In contrast, in the phase Ib trial of toripalimab in the treatment of patients with NENs (Ki-67 ≥ 10%) described above, patients with PD-L1 expression ≥ 10% had better ORR than those with PD-L1 < 10% (50.0% *vs* 10.7%, P = 0.019)[30]. Therefore, it appears that considering merely the negative or positive expression of PD-L1 is insufficient for identifying GEP-NET patients who may benefit from ICIs and that quantifying PD-L1 expression appears to be more significant. Furthermore, only 10% of tumors expressed PD-L1 in a large cohort of 136 patients with G3 GEP-NENs and those tumoral cells with positive PD-L1 were all in poorly differentiated cases[52]. Therefore, it is necessary to combine PD-L1 with other predictive biomarkers to better predict the population that may benefit from immuno-

therapy.

For other biomarkers, both high TMB (TMB-H) and microsatellite instability-high (MSI-H)/deficient mismatch repair protein (dMMR) are independent adverse prognostic factors for NENs[53] and also have an important predictive value. Wang *et al*[54] reported that 50% of the 18 Chinese patients with NETs had TMB-H. In a NET cohort analyzed by Patel *et al*[15], found no difference in the PD-L1 positivity rate between G3 and G1/G2 tumors, while the TMB-H rate was significantly higher in G3 NENs independent of tumor origin. Large samples of clinical and genomic data demonstrated that TMB-H was associated with increased survival in patients treated with ICI across various cancer types[55]. Duan *et al*[56] discovered that half of pNEN patients had decreased expression of MMR, another important biomarker. Venizelos *et al*[57] recently reported that MSI occurred in only 5.3% (8/152) of GEP-NEC patients and 3.4% (1/29) of G3 GEP-NET patients.

Pre-treatment assessment of one or more of these biomarkers provides a new perspective for screening good responders to immunotherapy.

CONCLUSION

In this minireview, data from prospective clinical trials and retrospective studies on the role of immunotherapies on G3 GEP-NET has been screened and reviewed. For ICI monotherapy, the efficacy of pembrolizumab, spartalizumab, and avelumab on G3 GEP-NETs is very limited. Only toripalimab has shown a moderate clinical activity on NENs with Ki-67 ≥ 10%, PD-L1 expression ≥ 10%, or high TMB. In addition, the ORR of well-differentiated tumors treated with toripalimab was slightly better than that of poorly differentiated cancers. Toripalimab and surufatinib therapy did not cause disease remission in 4 patients with G3 NETs. However, the treatment did not prevent remission in NEC and G1-2 NETs. Therefore, these regimens could potentially be effective in the treatment of G3 GEP-NETs if a large number of subjects are included. In other studies, the N+I therapy achieved PD in 2 of 3 patients with G3 NET as well as moderate efficacy in high-grade NENs. These results suggest that N+I may represent an extremely promising treatment option for G3 NET.

At present, all clinical trials investigating G3 GEP-NET are either phase I or phase II studies with small sample sizes. In this study, several challenges were encountered when collecting and evaluating data on the efficacy of immunotherapies for G3 GEP-NETs. According to the 2010 WHO classification, the inclusion of high-grade NETs in studies of NECs, the lack of Ki-67 index data in well-differentiated tumors, and the inclusion of tumors derived from lung, esophageal or unknown tissue all contribute to significant heterogeneity in reported results. Additionally, the review mainly focuses on the ORR to evaluate the potential role of immunotherapies in the treatment of G3 NETs. This is because the majority of prospective studies are ongoing and the survival data are in their infancy. Therefore, it is necessary to conduct prospective clinical trials with a large sample size of pathologically confirmed G3 GEP-NETs to evaluate the efficacy of the above immunotherapies. Besides, referencing data from important biomarkers facilitates the screening of patients who may benefit.

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