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...
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 capécitabine 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 reviewed yet.

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%, \( P = 67% \), \( P < 0.1 \)], a total DCR of 42%, a mPFS of 4.1 mo (95%CI: 2.6-5.4; \( P = 96% \), \( P < 0.1 \)), and a mOS of 11 mo (95%CI: 4.8-21.1; \( P = 98% \), \( P < 0.1 \))[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. 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 chemotheraphy 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, excluding lung origin | 6 G3 NENs                     |
| NCT02955069[25]              | Spartializumab | 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 G1-NEC, 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 recruiting | G3 NENs: after first-line | 29 G3 NENs: 16 NEC |

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| Study ID | Therapy | Trial Type | Summary | Phase | ORR | Baseline | Studied | Results |
|----------|---------|------------|---------|-------|-----|----------|---------|---------|
| NCT03278405 [38] | Avelumab | IIA | A pilot study of avelumab in unresectable/metastatic, progressive, poorly differentiated grade 3 neuroendocrine carcinomas (NET001) | IIA | 10 | March 12, 2020 | Completed | NECs: Poorly-differentiated, GI or lung origin, have received 0-2 prior lines of systemic therapy, excluding MANEC |
| NCT03278397 [28] | Avelumab | II | A phase II study of avelumab in unresectable/metastatic, progressive grade 2-3 neuroendocrine tumors (NET-002) | II | 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 |
| 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) | II | Best response | 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 | I | AEs, MTD | December 20, 2021 | Recruiting | NECs: G1-3 NET, NEC |
| NCT04169672 [40] | Toripalimab + surufatinib | II | A phase II, open-label, single-arm, multicenter study of the efficacy and safety of surufatinib combined with toripalimab in patients with advanced solid tumors | II | AEs, ORR | February 28, 2022 | Recruiting | NECs: Refractory to first-line chemotherapy |
| NCT03475953 | Avelumab + regorafenib | I/II | A phase I/II study of regorafenib plus avelumab in solid tumors (REGOMUNE) | I/II | Phase I: Recommended dose of regorafenib; Phase II: ORR, PFS | May 2022 | Recruiting | G2/3 GEP-NETs |
| NCT03290079 | Pembrolizumab + lenvatinib | II | Phase II study of pembrolizumab and lenvatinib in advanced well-differentiated neuroendocrine tumors | II | ORR | 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 surufatinib + tislelizumab | Ib/II | DLT, ORR | April 30, 2023 | Recruiting | G1/2 NETs: Thoracic or - |
| Trial Number | Treatment | Phase | Description | ORR | Status | Key Details |
|--------------|-----------|-------|-------------|-----|--------|-------------|
| NCT04207463 | Surufatinib + tislelizumab | II | A phase II, open, single-arm, multi-cohort, multicenter study of surufatinib and tislelizumab in subjects with advanced solid tumors | 150 | May 30, 2021 | Recruiting; G1/2 GEP-NETs, have progressed on at least one line of standard therapy |
| NCT03074513 | Atezolizumab + bevacizumab | II | A phase II, single-arm open-label study of the combination of atezolizumab and bevacizumab in rare solid tumors | 164 | March 31, 2021 | Active, not recruiting; G1/2 NETs; pNET cohort and epNET cohort containing typical or atypical carcinoid if originating in lung |
| NCT02923934 | Nivolumab + ipilimumab | II | A phase II clinical trial evaluating ipilimumab and nivolumab in combination for the treatment of rare gastrointestinal, neuroendocrine and gynaecological cancers (CA209-538) | 120 | December 2023 | Active, not recruiting; NEENs: G1-3 NETs, NECs, GEP or lung origin; 10 GEP-NENs: 7 pNENs (3 G3 pNETs, 2 pNECs, 2 G2 pNETs); 3 GL-NENs (1 gastro-oesophageal junction NEC, 1 colonic NECs, 1 G1 gastric NET) |
| NCT02834013 | Nivolumab + ipilimumab | II | A prospective, open-label, multicenter phase II basket clinical trial of ipilimumab plus nivolumab across multiple rare tumor cohorts (DART) | 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 |
| NCT04969887 | Nivolumab + ipilimumab | II | Ipilimumab and nivolumab combination therapy in patients with selected immunotherapy sensitive advanced rare cancers (MORT-CIRCUIT) | 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) | 180 | September 2023 | Recruiting; NECs: Poorly differentiated, refractory, pulmonary or GEP, excluding SCLC |
| NCT03109274 | Tremelimumab + durvalumab | II | A phase II study of durvalumab (MED14736) plus tremelimumab for the treatment of patients with advanced neuroendocrine neoplasms of gastroenteropancreatic or lung origin (DUNE) (GETNE 1601) | 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 |

Cohort 1-3: CBR at 9 m; Cohort 4: OS at 9 mo; 123 NENs (Cohort 1: 27 typical/atypical lung carcinoid; Cohort 2: 31 G1/G2 G1-NENs; Cohort 3: 32 G1/G2 pNENs; Cohort 4: 33 G3 NEN of GEP or unknown primary site)
| NCT Number     | Treatment                                                                 | Study Design | OUTCOMES | Start Date | Status                  | Eligibility                                                                 |
|---------------|---------------------------------------------------------------------------|--------------|----------|------------|-------------------------|----------------------------------------------------------------------------|
| NCT04079712   | Nivolumab + ipilimumab + cabozantinib                                      | II           | ORR      | 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           | ORR      | December 31, 2021 | Active, not recruiting | NECs: Any grade or primary site                                             |
| NCT03980925   | Nivolumab + platinum-doublet chemotherapy                                  | II           | OS at 12 mo | December 2022   | Recruiting             | G3 NECs: GEP or unknown primary site                                        |
| NCT0365791[59] | Spartalizumab + LAG525                                                     | II           | CBR at 24 wk | September 17, 2020 | Completed               | NETs: Well-differentiated, relapsed and/or refractory to available standard of care therapies |
| NCT03043664[60] | Pembrolizumab + lanreotide depot                                           | Ib/II        | ORR      | September 1, 2021 | Active, not recruiting | G1-2 GEP-NETs: Had progressed on a prior SSA                                |
| NCT04525638   | Nivolumab + 177Lu-DOTATATE                                                  | II           | ORR      | September 30, 2024 | Recruiting             | G3 NECs: GEP or unknown primary site, well-differentiated or poorly-differentiated. |
| NCT04701307   | Dostarlimab + niraparib                                                    | II           | ORR      | 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   | Pembrolizumab + 177Lu-DOTATATE; Pembrolizumab + TAE; Pembrolizumab + 90Ytrium-Microsphere Radioembolization | II           | ORR      | March 31, 2024   | Recruiting             | G1-3 NETs: Well-differentiated, any primary site and unknown primary site, have liver metastases |
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| NCT03879694 | SVN53-67/M57-KLH peptide vaccine (SurVaxM) +Octreotide | 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 | 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 adeno-neuroendocrine 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; 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 G3 NETs 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 G3 NETs. 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 G1-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), 177Lu-DOTATATE (PRRT), and liver-directed therapies (Transarterial Embolization or 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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