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EDITORIAL

Treatment strategies for advanced neuroendocrine neoplasms: current status and future prospects

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Neuroendocrine neoplasms (NENs) are relatively rare tumors that arise from peptidergic neurons and neuroendocrine cells. NENs are highly heterogeneous and can occur in any part of the body, with a particular prevalence in the digestive system. NENs consist of a range of tumor types and the biological behaviors exhibit significant differences. NENs are classified into well-differentiated neuroendocrine tumors (NETs) and poorly differentiated neuroendocrine carcinomas (NECs). NETs can be further classified and graded into the following three categories: low-grade NETs, grade 1 (NET G1); intermediate-grade NET G2; and high-grade NET G3. NECs include large cell-type NEC (LCNEC) and small cell-type NEC (SCNEC), both of which are considered high grade. Currently, the main treatments for advanced NENs are biological treatments, targeted therapy, chemotherapy, and newer treatments that are still under development, such as immunotherapy and peptide receptor radionuclide therapy (PRRT). However, owing to the rarity of NENs, pharmaceutical company investment is limited and few phase III studies have targeted advanced NENs. Most current research consists of investigator-initiated phase I and II clinical trials or large-scale retrospective studies. NEN treatment should be chosen carefully because it is cumbersome and complicated, as indicated above. Herein, we comprehensively summarize the clinical application status and research progress for advanced NEN treatment regimens, especially for advanced NETs, which may help to create awareness on NENs among medical professionals across specialties.

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Treatment of NETs

The biological treatments for NETs include interferon-α (IFN-α) and long-acting somatostatin analogs (SSAs). Phase III trials (FNCLCC-FFCD 9710 and SWOG S0518) did not demonstrate a significant therapeutic advantage with IFN-α[1,2]. Currently, IFN-α is only recommended in combination with an SSA as a second-line treatment for patients with a refractory NET and carcinoid syndrome. Somatostatin is a 14-amino acid peptide that inhibits the release of pituitary growth hormone by acting on different targets through five subtypes of somatostatin receptors (SSTRs). Synthetic SSAs are now considered the standard treatment for functional NETs that originate from any anatomic site. Representative SSA drugs include octreotide and lanreotide. Two landmark phase III clinical trials (PROMID and CLARINET) showed a statistically significant prolongation of time to progression/progression-free survival (TTP/PFS) upon SSA treatment compared to placebo[3,4]. A *post hoc* analysis of a phase III clinical trial revealed that pasireotide, a new-generation SSA, achieved a median progression-free survival (mPFS) of 11.8 months in patients with metastatic NETs compared to 6.8 months in the high-dose octreotide control group[5]. NET molecular-targeted therapies currently fall into two categories [mammalian targeting of rapamycin (mTOR) inhibitors, and tyrosine kinase inhibitors (TKIs)]. An mTOR inhibitor, such as everolimus, inhibits cell metabolism, growth, proliferation, and angiogenesis, which in turn inhibits NETs. TKI drugs, such as sunitinib and surufatinib, primarily inhibit vascular endothelial growth factor (VEGF) and the VEGF receptor pathway to suppress NET angiogenesis and tumor proliferation. **Table 1**

Table 1 Results of phase III trial of gastroenteropancreatic neuroendocrine tumors

Trial	Study drug	Targets	Study population	Number	Efficacy
NCT00510068 (RADIANT-3)[6]	Everolimus *vs.* placebo	mTOR	pNET	410 (207/203)	mPFS: 11.0 *vs.* 4.6 mos; HR = 0.35, $P < 0.001$; ORR: 5% *vs.* 2%
NCT01524783 (RADIANT-4)[7]	Everolimus *vs.* placebo	mTOR	Lung & GI-NET	302 (205/97)	mPFS: 11.0 *vs.* 3.9 mos; HR = 0.48, $P < 0.00001$; ORR: 2% *vs.* 1%
NCT00428597 (A6181111)[8]	Sunitinib *vs.* placebo	VEGFR-1, VEGFR-2, VEGFR-3, *c-KIT*, PDGFR-α, and PDGFR-β, *FLT-3*, CSF1R	pNET	171 (86/85)	mPFS: 11.4 *vs.* 5.5 mos; HR = 0.42, $P < 0.001$; ORR: 9.3% *vs.* 0%
NCT02589821 (SANET-p)[9]	Surufatinib *vs.* placebo	VEGFR-1, VEGFR-2, VEGFR-3, FGFR-1, CSF-1R	pNET	172 (113/59)	mPFs: 10.9 *vs.* 3.7 mos; HR = 0.49, $P = 0.0011$; ORR: 19% *vs.* 2%
NCT02588170 (SANET-ep)[10]	Surufatinib *vs.* placebo	VEGFR-1, VEGFR-2, VEGFR-3, FGFR-1, CSF-1R	epNET	198 (129/69)	mPFS: 9.2 *vs.* 3.8 mos; HR = 0.33, $P < 0.0001$; ORR: 10% *vs.* 0%

NET, neuroendocrine tumor; pNET, pancreatic NET; ep, extra-pancreatic NET; mTOR, mammalian targeting of rapamycin; GI, gastrointestinal; mPFS, median progression-free survival; HR, hazard ratio; mos, months; ORR, objective response rate; VEGFR, vascular endothelial growth factor receptor; PDGFR, platelet-derived growth factor receptor; CSF1R, colony-stimulating factor-1 receptor; FGFR, fibroblast growth factor receptor.

summarizes the results of a phase III trial involving gastroenteropancreatic NETs[6-10]. **Table 2** summarizes the results of drugs in development. Some progress has been made in molecular-targeted therapy for NETs in recent years, but few drugs in development have shown clinically significant advantages over approved drugs[11-14].

PRRT is a promising new treatment that was developed in the past two decades. PRRT uses radiolabeled peptides to target tumor cells expressing SSTR. Receptor–peptide complexes are internalized through endocytosis and accumulate within the cell. This process allows the conjugated radionuclide to emit local radiation that causes DNA damage and tumor cell death. The PRRT drugs that are used most frequently are 177Lu or 90Y-labeled SSAs. The NETTER-1 phase III study demonstrated that 177Lu-dotatate significantly prolongs the mPFS (28.4 months *vs.* 8.5 months) and the objective response rate (ORR) (19% *vs.* 3%) for patients with progressive midgut NETs compared to high-dose octreotide[15]. PRRT is a second-line treatment option for SSTR-positive NETs but PRRT is only recommended for patients with low-grade and low-burden NETs.

Chemotherapy is generally considered for NET patients with a high Ki-67 index (> 15%) and large tumor burden. Capecitabine plus temozolomide is the most frequently used regimen for NET, although the benefit varies depending on the tumor origin. The mPFS for lung NETs is 9–13 months and 16.1 months for G1/G2 GEP-NETs. Some studies have explored other NET chemotherapy regimens. For example, a multicenter retrospective study investigated the FOLFOX regimen in well-differentiated progressive gastrointestinal NETs. The ORRs for patients with pancreatic (p)NETs, small intestine NETs, and gastric NETs were 30%, 12.5%, and 14%, respectively[16]. The STEM trial included patients with unresectable/metastatic, pancreatic, or non-pancreatic NETs. Among extra-pancreatic (ep)NET patients, the mPFS in the S-1/temozolomide plus thalidomide and S-1/temozolomide groups were 6.8 and 7.4 months, respectively. Among patients with pNETs the mPFS was 16.2 months. Therefore, patients with the MGMT 0/+1 mutation are at an advantage compared to the rest of the population[17].

Currently, immunotherapy for NETs is both a hot topic and a challenge. The use of immune checkpoint inhibitors (ICIs) as monotherapy has limited efficacy in treating NETs. The Keynote-028 study reported an ORR of 12% for pembrolizumab in a cohort with carcinoid syndrome and only 6.3% in patients with pNETs[18]. The Keynote-158 study showed that

Table 2 Results of drug trials in development for neuroendocrine tumors

Trial	Phase	Study drug	Targets	Study population	Number	Efficacy
NCT01280201 (PAZONET)[11]	II	Pazopanib	VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-α, PDGFR-β, and *c-Kit*	pNET & GI-NET	44	mPFS: 9.5 mos (pNET 12.8 mos, GI-NET 10.0 mos) ORR: 9%
NCT01435122[12]	II	Axitinib	VEGFR-1, VEGFR-2, VEGFR-3	Carcinoid tumors	30	mPFS: 26.7 mos ORR: 3%
NCT03375320[13] (CABINET)	III	Cabozantinib *vs.* placebo	*c-MET*, VEGFR2, *AXL*, *KIT*, *TIE2*, *FLT3*, *RET*	NET	203 (134/69)	mPFS: pNET 11.4 *vs.* 3.0 mos; ep-NET 8.3 *vs.* 3.2 mos
NCT02678780[14] (TALENT)	II	Lenvatinib	VEGFR-1, VEGFR-2, VEGFR-3, FGFR-1, FGFR-2, FGFR-3, FGFR-4, PDGFR-α, *KIT* and *RET*	pNET & GI-NET	111	pNET: ORR 44.2%; mPFS 15.6 mos GI-NET: ORR 16.4%; mPFs 15.7 mos

NET, neuroendocrine tumor; pNET, pancreatic NET; epNET, extra-pancreatic NET; GI-NET, gastric NET; mPFS, median progression-free survival; VEGFR, vascular endothelial growth factor receptor; PDGFR, platelet-derived growth factor receptor; FGFR, fibroblast growth factor receptor.

pembrolizumab has an ORR of only 3.7% and an mPFS of 4.1 months in NET patients who failed standard therapy[19]. There is a lack of convincing evidence to support ICI use in NETs.

Treatment of NECs

NECs are highly malignant and aggressive, and chemotherapy remains the first-line systemic treatment option. The median OS is only 11–12 months for metastatic NECs. The combination of etoposide and cisplatin (EP) or carboplatin (EC) is the standard first-line chemotherapy regimen for advanced or unresectable NECs. The NORDIC NEC retrospective study reported that first-line treatment with EP/EC had an ORR of 31% and a mPFS of 4 months[20]. Other first-line chemotherapy regimens have also been explored. For example, a phase II study in China and a phase III randomized controlled trial in Japan reported that irinotecan combined with cisplatin as first-line treatment for advanced gastrointestinal NECs had similar efficacy to EP[21]. The phase II randomized controlled NABNEC study evaluated nab-paclitaxel combined with carboplatin as a first-line treatment for gastrointestinal NECs. The study reported an ORR and 24-month overall survival (OS) rate of 53% and 25%, respectively, in the nab-paclitaxel combined with carboplatin group compared to 42% and 17%, respectively, in the control group (EP/EC regimen)[22]. The efficacy of second-line treatments for NECs has not been established. Indeed, most studies had small samples or were retrospective analyses providing low-level evidence. Therefore, there is no standard for second-line treatment of NECs. FOLFOX/FOLFIRI has been used as a second-line chemotherapy regimen with an ORR of approximately 30% and an mPFS of only approximately 4 months. The PRODIGE 41-BEVANCE study evaluated bevacizumab combined with FOLFIRI as a second-line treatment for NECs but reported no improvement in PFS or OS with the addition of bevacizumab[23].

NECs tend to have higher PD-L1 expression, $CD8^+$ lymphocyte infiltration, and tumor mutational burden (TMB) than NETs. Despite success in the treatment of partial NECs, such as small cell lung cancer and Merkel cell carcinoma, most patients with NECs do not benefit from ICI monotherapy. Specifically, the disease control rate (DCR) is 20.7%–32% and a median overall survival (mOS) of only 4.2 months. Current research is also focused on combination therapies. Dual immune therapy has shown limited efficacy. Ipilimumab combined with nivolumab achieved an ORR of 44% but the mPFS was only 4 months in the NEC cohort of the phase II

Table 3 Results of combination therapy trials for neuroendocrine tumors

	Trial	Phase	Study drug	Study population	Number	Efficacy
SSA and TKI combinations	NCT01374451 (COOPERATE-2)[31]	Ⅱ	Everolimus plus pasireotide *vs.* everolimus	pNET	160 (79/81)	mPFS: 16.8 *vs.* 16.6 mos, HR = 0.991, *P* = 0.488; ORR: 20.3% *vs.* 6.2%
	NCT00412061 (RADIANT-2)[32]	Ⅲ	Everolimus plus octreotide *vs.* placebo plus octreotide	NET	429 (216/213)	mPFS: 16.4 *vs.* 11.3 mos, HR = 0.77, *P* = 0.026; mOS: 29.2 *vs.* 35.2 mos, HR = 1.17
	NCT01563354 (LUNA)[33]	Ⅱ	Everolimus plus pasireotide *vs.* everolimus *vs.* pasireotide	Carcinoids	124 (41/42/41)	mPFS: 11.8 *vs.* 12.5 *vs.* 8.5 mos, *P* > 0.005
Dual immune combinations	NCT02834013 (DART SWOG 1609)[24]	Ⅱ	Ipilimumab plus nivolumab	epNET	14	ORR: 0%
	NCT03095274 (Dune)[34]	Ⅱ	Durvalumab plus tremelimumab	Lung carcinoids G1/G2 GI-NET G1/G2 pNET G3 GEP-NET	123 (27/31/32/33)	mPFS: 5.6 *vs.* 5.8 *vs.* 5.5 *vs.* 2.4 mos; ORR: 11.0% *vs.* 0.0% *vs.* 6.3% *vs.* 9.1%
PD-1 inhibitor and VEGFR inhibitor combinations	NCT04169672[28]	Ⅱ	Surufatinib plus toripalimab	NET	19	mPFS: 9.6 mos; ORR: 21.1%
	NCT04169672[35]	Ⅱ	Atezolizumab plus bevacizumab	NET	40	mPFS: pNET 14.9 mos, epNET 14.2 mos; ORR: pNET 20%, epNET 15%

NET, neuroendocrine tumor; pNET, pancreatic NET; epNET, extra-pancreatic NET; GI-NET, gastric NET; GEP-NET, gastroenteropancreatic NET; mPFS, median progression-free survival; ORR, objective response rate; PD-1, programmed cell death-1; VEGFR, vascular endothelial growth factor receptor.

DART SWOG 1609 study[24]. The phase II NIPINEC trial reported that patients with advanced NECs who progressed after platinum-based chemotherapy and received ipilimumab plus nivolumab had an mPFS and mOS of 1.9 and 5.8 months, respectively[25]. Immunotherapy combined with chemotherapy has also enjoyed limited success. The phase II NICE-NEC study showed that first-line treatment for advanced NECs with nivolumab plus EP achieved an mPFS of only 5.7 months[26]. Another phase II study reported an ORR of 5% and an mPFS of only 2 months for pembrolizumab combined with paclitaxel or irinotecan as second-line treatment for patients with extra-pulmonary NECs[27]. A phase II basket study of the immune-targeted therapy combination, surufatinib plus toripalimab, in patients with advanced solid tumors reported an ORR of 23.8% in the NEC cohort with an mPFS of approximately 4 months after first-line progression[28].

Future prospects for NENs

There are several possible future prospects for SSA drugs. First, increasing the SSA dosage after progression on first-line treatment appears to be effective in extending the tumor control time. SSA resistance mechanisms are not fully understood but may be associated with SSTR downregulation or the emergence of tumor clones that lack SSTR expression. Increasing the SSA dose may saturate SSTRs in NETs, which may help overcome resistance. In phase II CLARINET FORTE study, which involved progressive NET patients who followed a standard lanreotide regimen, a dosage increase led to mPFS of 8.3 and 5.6 months in midgut NET and pNET patients, respectively[29]. In the phase III NETTER-1 trial, patients who progressed to first-line long-acting octreotide achieved an mPFS of 8.4 months when treated with high-dose octreotide (60 mg every 28 d)[15]. Second, SSAs have limited efficacy in NET patients with a high tumor burden. Reducing the hepatic tumor burden through local treatments, such as embolization, could prolong the effective duration of SSAs. A retrospective cohort study revealed that among patients with a liver metastatic tumor burden > 50%, the mPFS was significantly extended to 12.6 months in patients who achieved a complete response (CR) or partial response (PR) after transarterial embolization (TAE) followed by SSAs. This result was significantly longer than the 4.4 months reported in patients without remission[30]. Third, more prospective randomized controlled studies are warranted to determine whether dosage increases or switching to another therapy would be more beneficial as second-line treatment. In addition, studies are needed to evaluate whether SSAs should be continued when transitioning to other therapies.

New challenges will emerge for physicians as more drug options for NETs become available and different combination treatment strategies should be considered. **Table 3** summarizes the results of trials on combination therapy for NETs[24,28,31-35]. The primary aim of drug treatments for NETs is to control the symptoms of functional tumors and tumor proliferation regardless of the treatment strategy chosen. Neither SSAs nor targeted therapies have demonstrated ideal ORRs for patients with slow-growing tumors. Decisions must be made in these cases regarding the use of monotherapy or combination therapy, the order of drug administration according to treatment goals, and how to integrate drug treatments with locoregional therapies to maximize tumor shrinkage and prolong survival. High-quality studies are needed to answer these questions.

PRRT may be a potential first-line treatment option. The NETTER-2 trial enrolled patients with higher grade (G2 and G3), SSTR-positive, and advanced gastroenteropancreatic NETs (GEP-NETs). This trial compared the efficacy of 177Lu-dotatate plus LAR octreotide (30 mg) with high-dose LAR octreotide (60 mg) as first-line therapy. Combination therapy significantly improved the ORR (43% *vs.* 9.3%) and prolonged the mPFS (22.8 *vs.* 8.5 months) with 83% of patients showing tumor shrinkage[36]. Additionally, α-particle radionuclide therapy, such as RYZ101 and 212Pb-dotamtate, are emerging as new therapeutic options. However, many questions remain regarding PRRT, such as the optimal treatment timing, whether fixed or personalized dosing is preferable, how to select the appropriate radionuclide for different patients, and how to manage complications.

NEC treatment faces significant challenges but chemotherapy remains the first-line systemic treatment option. Single-agent immunotherapy has yielded poor results and multiple combination therapy strategies are still under clinical investigation. In recent years promising therapeutic targets, such as 4-1BB (also known as CD137) and DLL3 (delta-like ligand 3), have been discovered but clinical data are incomplete. We hope that future studies will provide new options for the clinical treatment of NEC patients.

Conclusions

The treatment of NETs is complicated by the broad organ origins and complex classification and grading systems. This

makes large-scale clinical studies challenging. Several key issues need to be addressed. First, NETs from different organs are often treated as a single disease and the differences between pNETs and epNETs are considered only in targeted drug selection. However, the efficacy of the same drug or treatment regimen can vary significantly depending on the organ of origin. Second, the treatment concept still follows the "sequential therapy" model used for other solid tumors, in which one drug or treatment regimen is followed by another drug or treatment regimen after failure. The efficacy and toxicity of different drugs vary in clinical practice and patient responses and tolerability to the same regimen differ. Future studies should explore the feasibility of treatment sequencing, maintenance therapy, and rechallenge therapy, as well as optimizing combination therapies and integrating other treatment modalities to maximize the efficacy of each drug. For poorly differentiated advanced NECs, chemotherapy remains the primary treatment option and some patients may benefit from combined chemotherapy and immunotherapy or immunotherapy alone. Additional research is needed to explore combination therapy strategies and possibly provide enhanced benefits for patients with NECs.

Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

Conceived and designed the analysis: Sisi Ye, Juan Li, Jianming Xu.
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