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REVIEW ARTICLE

Targeted Systemic Treatment of Neuroendocrine Tumors: Current Options and Future Perspectives

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Abstract

Neuroendocrine tumors (NETs) originate from the neuroendocrine cell system in the bronchial and gastrointestinal tract and can produce hormones leading to distinct clinical syndromes. Systemic treatment of patients with unresectable NETs aims to control symptoms related to hormonal overproduction and tumor growth. In the last decades prognosis has improved as a result of increased detection of early stage disease and the introduction of somatostatin analogs (SSAs) as well as several new therapeutic options. SSAs are the first-line medical treatment of NETs and can control hormonal production and tumor growth. The development of next-generation multireceptor targeted and radiolabelled somatostatin analogs, as well as target-directed therapies (as second-line treatment options) further improve progression-free survival in NET patients. To date, however, a significant prolongation of overall survival with systemic treatment in NET has not been convincingly demonstrated. Several new medical options and treatment combinations will become available in the upcoming years, and although preliminary results of preclinical and clinical trials are encouraging, large, preferrably randomized clinical studies are required to provide definitive evidence of their effect on survival and symptom control.

Key Points

Therapeutic options for symptom control in functioning neuroendocrine tumors (NETs) are still limited, especially in progressive disease

Novel targeted systemic treatment options have become available for NET patients in the last years, but their effect on overall survival is still controversial.

Randomized clinical trials that compare, combine, and sequence current and potential novel therapies are pressingly required.

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1 Introduction

The endocrine system is composed of neuroendocrine cells dispersed throughout the entire body. These cells can be found in isolation or may form small aggregates [1]. Neuroendocrine tumors (NETs) originate from these cells [1, 2], and this heterogeneous group of neoplasms displays a wide range of biological behavior ranging from benign behavior with a life expectancy of decades to highly malignant clinical behavior with a very limited life expectancy [3]. Tumor heterogeneity is also reflected in the categorization of these tumors, which includes primary tumor localization (e.g., lung, pancreas, stomach, small bowel, colon), tumor grade, functional activity, disease stage, and susceptibility to drug treatment [4, 5]. NETs are histologically graded into well differentiated (grade 1, 2, or 3 NETs) or poorly differentiated (neuroendocrine carcinomas) tumors [5]. Locoregional or oligometastatic well-differentiated NETs are candidates for surgical resection with curative intent. However, a considerable subset of patients presents with irresectable or metastasized disease and consequently requires palliative systemic treatment.

According to the last National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) statistics, the incidence of NETs has increased substantially (1.09/100,000 persons in 1973 to 6.98/100,000 in 2012),

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especially for lung, small intestinal, and rectum NETs. In this context, the rate of patients with localized disease at the time of diagnosis has increased in the last years, which allowed for improved surgical resection rates and prognosis. However, survival has also improved for patients with advanced stages of gastroenteropancreatic-(GEP-)NETs, which is partially explained by the introduction of somatostatin analogs (SSAs) [6].

SSAs are the cornerstone of systemic treatment of well-differentiated, locally advanced or metastatic NETs [7–9]. SSAs act through binding to G-protein-coupled somatostatin receptors (SSTRs), which are broadly expressed in NETs and can modulate hormone secretion and tumor cell proliferation [10–12]. Although SSAs can induce sustained disease stabilization, resistance to treatment frequently occurs after prolonged use, even when dose-intensification has been pursued. Various alternative approaches can be considered here, e.g., the use of radiolabeled SSAs [13], the application of specific inhibitors of various tumor-cell signal transduction pathways and/or angiogenesis [14, 15], and the use of chemotherapy [16]. Additionally, new therapeutic options for functioning NETs have been developed [17, 18], and several novel treatments are currently under study [19, 20]. Considering the more recent advances in systemic treatment in NETs, an overview of the currently available treatment options for advanced functional as well as non-functional NETs is presented, as well as an overview of novel therapeutic options and clinical trials. We will not discuss systemic chemotherapy or neuroendocrine carcinomas.

2 Control of Hormonal Overproduction

NETs may cause specific clinical syndromes due to an overproduction of hormones and bioactive peptides. The incidence of functioning NETs ranges from 0.01–8.4 cases per 100,000 per year, depending on the secreted hormone. Carcinoid syndrome is the most frequent hormone-related syndrome within NETs (2–8.4 new cases/100,000/year) and is predominantly encountered in patients with metastasized midgut NETs [21, 22]. SSAs are considered to be the preferred first-line treatment option in functionally active NETs, including those associated with the carcinoid syndrome and functional pancreatic neuroendocrine tumors (PNETs) [11, 23]. The mechanisms of action of current medical options for functioning NETs are depicted in Fig. 1.

2.1 Carcinoid Syndrome (CS)

Carcinoid syndrome (CS) is mediated by several hormones, especially serotonin, and comprises several symptoms including flushing (94%), diarrhea (78%), carcinoid heart disease (CHD) (53%), and abdominal pain (51%) [24]. The role of SSAs on this often highly symptomatic secretory diarrhea and flushes was initially described in 1978 [25–27]. Since then, short-acting octreotide has been considered as a treatment option for carcinoid syndrome. The efficacy of short- and long-acting octreotide is similar once steady-state circulating concentrations of octreotide are achieved [27, 28]. Long-acting preparations of SSAs are widely used, probably due to their efficacy, but also to the comfortable administration every 28 days (in short-acting preparations, drug administration every 8 h may limit treatment compliance). SSAs improve flushes and diarrhea in 53–75% and 45–80% of cases, respectively [29, 30]. Long-acting octreotide and lanreotide similarly reduce urinary 5-hydroxyindoleacetic acid (u5-HIAA) and improve quality of life in NET patients [29]. Both octreotide and lanreotide are generally well tolerated, and side effects include gastrointestinal discomfort, headache, hyperglycemia, and the formation of bile stones [29].

Despite the effectiveness of SSAs, loss of response can occur after prolonged use. Tachyphylaxis, downregulation of cell surface SSTRs, and development of antibodies to SSAs have been hypothesized to underlie treatment resistance to SSAs [31–33]. In patients with refractory symptoms, intensified schedules consisting of either increased dose or increased frequency of administration have been found to control symptoms in about 40–81% of patients, without additional adverse events [34, 35]. Addition of short-acting octreotide (ranging from 100 to 500 µg every 8 h) is an alternative approach in case of treatment-refractory disease [36, 37]. In addition, favorable clinical response on carcinoid syndrome-related symptoms has also been reported in patients after treatment with peptide receptor radionuclide therapy (PRRT) [38, 39].

The use of serotonin-3-receptor antagonists (ondansetron) [40] and antidiarrheal drugs (loperamide) in combination with SSAs may improve episodes of diarrhea [41]. Pasireotide, a SSA with affinity to multiple SSTRs, has also been tested in patients with octreotide LAR-resistant tumors. Pasireotide showed efficacy in 33% of patients when administered at 150 µg twice daily, escalated to a maximum dose of 1200 µg per day [42]. However, a randomized phase III study of pasireotide LAR versus high-dose (40 mg) octreotide LAR for symptom control in patients with advanced GEP-NETs, whose disease-related symptoms were uncontrolled by first-generation SSAs at maximum approved doses, failed to show superiority of pasireotide LAR [43]. α-Interferon in combination with octreotide has been suggested as an effective treatment for symptom control, but unfortunately the use of this combination is limited due to the high rate of adverse effects attributed to α-interferon [44].

Recently, telotristate etiprate, a novel inhibitor of tryptophan hydroxylase, the rate-limiting enzyme in the

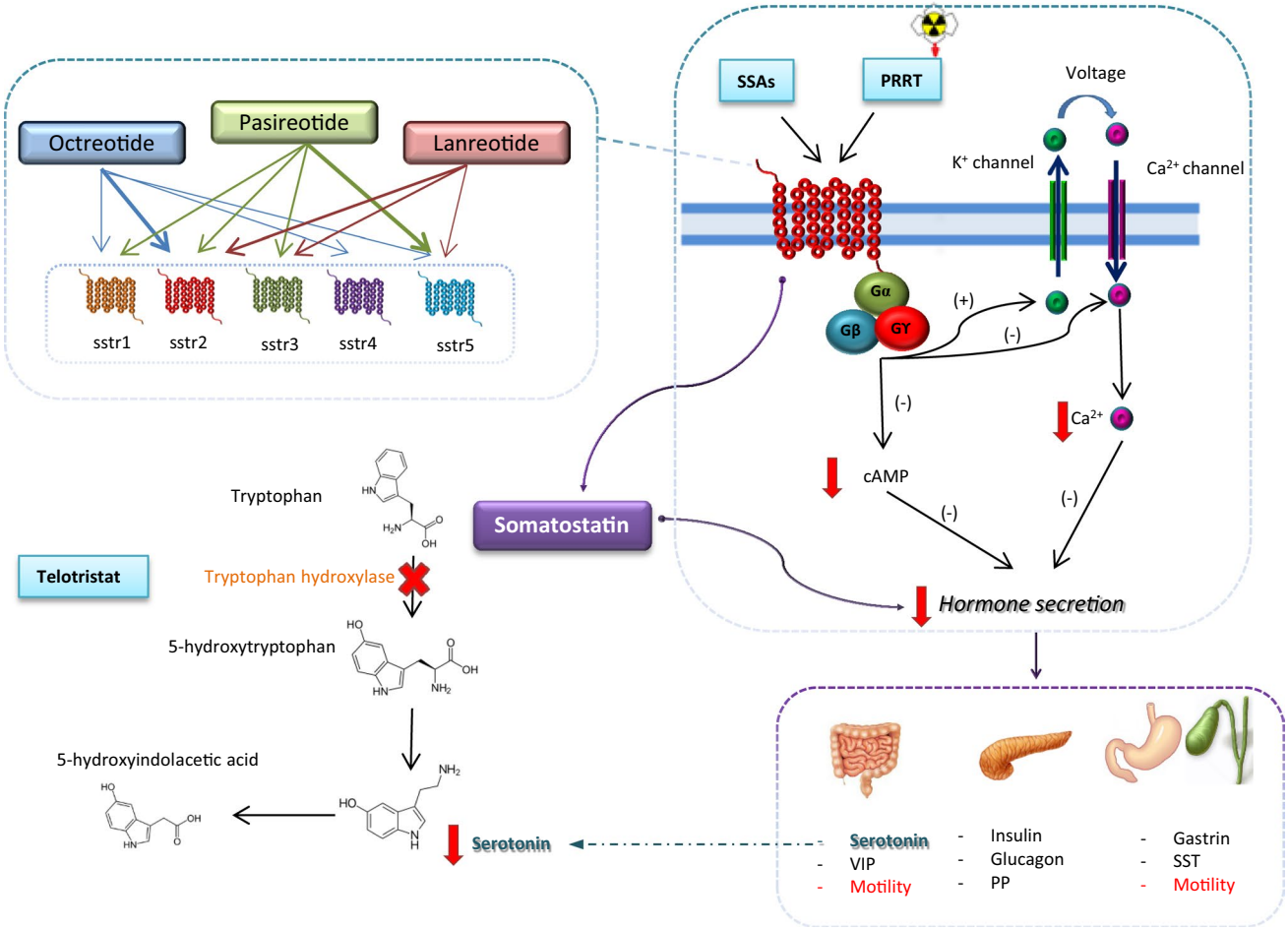


Fig. 1 Current medical treatment for symptoms control in neuroendocrine tumors. Short- and long-acting and radiolabeled somatostatin analogs bind to G-protein linked receptors on the cell surface with variable affinity. Decreases in cAMP and intracellular calcium levels inhibit hormone release. Somatostatin influences hormone secretion and motility in the whole gastrointestinal tract. Serotonin production may also be decreased by telotristat, which inhibits the rate-limiting step in the serotonin secretion (the enzyme tryptophan hydroxylase). *sstr* somatostatin receptor, *SSAs* somatostatin analog, *PRRT* peptide receptor radionuclide therapy, *cAMP* cyclic adenosine monophosphate, *VIP* vasoactive intestinal peptide, *PP* pancreatic polypeptide, *SST* somatostatin

biosynthesis of serotonin, has been developed [45]. This drug is able to suppress serotonin production in patients with NETs, as indicated by a decrease in u5-HIAA, with a concomitant partial improvement of diarrhea [17, 18, 46]. An international, multicenter, randomized, double-blind, placebo-controlled phase III trial (TELESTAR) reported a reduction of approximately 40% of bowel movements per day using telotristat etiprate doses of 750–1500 mg [45]. Furthermore, reductions of ≥ 30% in u5-HIAA levels have been reported with this drug [18, 47]. In this sense, a higher decrease in u5-HIAA has been associated with better improvement in bowel movements [18]. Recently, the phase III companion study TELECAST reported a statistically significant reduction in bowel movements in about 40% of patients, even in patients who were not on SSAs therapy. Unfortunately, the lack of patients in this last category (or that were assigned to the placebo group) limits conclusions in this respect [17]. Importantly, stool form improved in 20% and flushing in 27% of cases [18]. It seems therefore that a subset of patients with midgut NETs treated with SSAs may benefit from telotristat etiprate. Some adverse effects have been reported (including increase in transaminases and gastrointestinal symptoms, especially nausea) not resulting in treatment discontinuation [18, 45]. Some preclinical studies suggest that telotristat etiprate does not cross the blood-brain barrier ([Lexicon, unpublished observations in [18]). The TELESTAR study reported a higher incidence of depression-related events in patients receiving telotristat ethyl 500 mg three times per day, but not in those patients receiving 250 mg three times per day (similar incidence to placebo) [45]. This finding was not observed in the TELECAST study, however [17]. Finally, lowering circulating serotonin levels by telotristat etiprate may also be important to counteract the development of NET-associated cardiac

and mesenterial fibrosis, in which serotonin is thought to play a major role [48, 49].

2.1.1 Carcinoid Heart Disease

Tumor-secreted vasoactive hormones may also produce the deposition of plaques on the endocardial surfaces of valve leaflets, the subvalvular area, and cardiac chambers, affecting especially the right side of the heart, and resulting in carcinoid heart disease (CHD) [50]. CHD affects about 50% of patients with CS [51]. SSAs and/or tumor-debulking procedures may improve the hemodynamic impact of tumor vasoactive agents on CHD [28, 52, 53], but there is no convincing evidence that these treatment options can stop the progression of CHD [54].

The initial treatment of decompensated CHD consists of loop diuretics, fluid and salt restriction, and compression stockings. However, in advanced stages these treatments may become ineffective [55]. In those cases, cardiac valve surgery or balloon valvuloplasty is recommended [50]. When surgery is required, continuous octreotide infusion (50–100 μg/h) should be administered 2 h before until 24 h after the surgical procedure in order to prevent carcinoid crisis and its complications [56]. Antihistaminic drugs and corticosteroids may also be used before surgery [55], whereas the use of drugs (opioids, dopamine, adrenaline/epinephrine) that precipitate the release of vasoactive products should be avoided [56, 57]. In addition, the effect of telotristat etiprate in CHD should also be evaluated.

2.2 Insulinoma

Most insulinomas are small, benign tumors that can be surgically cured. Unfortunately, the clinical management of patients with metastatic insulinomas may be difficult. Apart from oral or intravenous glucose administration, several medical options are available to treat hypoglycemia in the preoperative setting or in case of metastatic disease. Diazoxide is a well-known drug to treat hypoglycemia in patients with insulinomas. It is a benzothiadiazide derivative that inhibits insulin secretion via ATP-dependent potassium channels in pancreatic β-cells. It also increases hepatic glucose production and inhibits tissue glucose uptake, improving hypoglycemia in 50–60% of cases [58–62]. It should be initiated in low doses (150–200 mg/day) administered two or three times daily until a maximum of 600–800 mg. If after 2–3 weeks of treatment any clinical improvement is observed, diazoxide may be stopped [63, 64]. Adverse effects are observed in about the half of patients and include water retention, hirsutism, weight gain, nausea, emesis, diarrhea, abdominal pain, headache, and rash [58, 59, 65].

SSAs (octreotide LAR and lanreotide autogel) are preferably used in malignant insulinomas, where the activation of SSTR (if expressed) decreases insulin release [66]. Unfortunately if SSTR expression is low or absent, SSAs may paradoxically lower blood glucose levels by suppressing glucagon release [60]. Insulin secretion is also inhibited via the SSTR type 5 (SSTR5) [67]. Since the affinity of pasireotide for SSTR5 is 30- to 40-fold higher when compared with octreotide [68], pasireotide may be an alternative therapeutic option in malignant insulinomas. Some cases reports described an appropriate glucose control with pasireotide in insulinomas resistant to other treatment options including octreotide LAR, everolimus, or chemotherapy [69, 70].

Blood glucose normalization in patients with malignant insulinomas has also been reported after treatment with everolimus when previous treatment options (octreotide LAR, chemotherapy, PRRT, or radiofrequency ablation) failed to achieve appropriate glucose control [65, 71, 72]. Clinical effect may be achieved after 2 weeks of treatment with 10 mg everolimus per day [63]. Everolimus can probably decrease insulin release through the AMP-activated protein kinase (AMPK)/c-Jun N-terminal kinase (JNK)/FoxO pathway, and it may also induce peripheral insulin resistance by downregulation of glucose transporter 1 (GLUT1) via reduced transcription and translation [71, 73–75].

PRRT can also be a successful therapeutic alternative in metastatic insulinomas with SSTR expression [76]. In a small patient series PRRT induced stable disease for 18–50 months and no hypoglycemic episodes occurred during that period [76]. Clinical improvement despite the presence of the tumor suggested a sustained effect of PRRT on insulin secreting machinery [60].

2.3 Glucagonoma

This rare tumor originating from α-pancreatic cells may cause the glucagonoma syndrome, which is characterized by the presence of necrolytic migratory erythema (NME), diabetes mellitus, and weight loss; other symptoms include anemia, glossitis, steatorrhea, diarrhea, venous thrombosis, and neuropsychiatric disturbances [77]. If surgery is performed, resection of the tumor load of at least 70–90% is necessary for symptom control, which may be difficult in several cases. Clinical symptoms may improve with SSAs (octreotide and lanreotide) [77]. Specifically, the NME may improve despite the persistence of elevated serum glucagon levels [78]. Pasireotide has also been suggested as an appropriate therapeutic option in octreotide-resistant tumors [77, 79]. In addition, sunitinib and everolimus have been reported as successful treatment options in these functioning tumors and both have been associated with increased progression-free survival (PFS) when compared to placebo [80, 81]. PRRT with ^{90}Yttrium-DOTATOC or ^{177}Lu-DOTATATE may induce disease stabilization or regression with subsequent symptom control [82], but series focusing only on glucagonomas are still lacking.

2.4 Gastrinoma

Gastrinomas are sporadic in 75% of cases. In these tumors, surgery is curative only in about 60% [83]. Surgical resection is also controversial in patients with multiple endocrine neoplasia syndrome type I due to a low probability of cure [84]. Consequently, medical treatment is necessary in a considerable number of patients [85].

Gastric hypersecretion and related symptoms should be treated with high-dose H^+-K^+-ATPase proton-pump inhibitors (PPIs) [83]. Serum levels of vitamin B12 and iron should be monitored at least once a year [86, 87].

Since SSTRs are widely expressed in gastrinomas [88], SSAs (octreotide and lanreotide) effectively suppress gastrin secretion and decrease or normalize gastric acid secretion in over half (50–100%) of gastrinoma patients [86, 89–91]. Their use has been associated with tumor stabilization in 47–75% of patients [91, 92], and SSAs may be combined with chemotherapy in metastasized gastrinomas [93]. In addition, SSAs may prevent the enterochromaffin-like cell hyperplasia or the development of gastric type 2 NETs, which are related to hypergastrinemia [94]. IFN-α (5×10^6 IU/day) improved clinical symptoms caused by hypergastrinemia only in stabilized tumors. Unfortunately, side effects frequently require dose reduction or drug withdrawal [85]. Furthermore, PRRT with radiolabeled beta emitting SSAs can lead to long-lasting (> 1 year) tumor responses in a very high number of patients and also leads to symptomatic improvement [50, 95].

2.5 Vasoactive Intestinal Polypeptide (VIP)oma, Somatostatinoma

Functioning NETs that release vasoactive intestinal polypeptide (VIP) have an incidence of 1:10 million persons/year. These tumors produce watery diarrhea, accompanied by severe hypokalemia, and hypo- or achlorhydria. In contrast, somatostatinomas may be asymptomatic or present with diabetes mellitus, cholelithiasis, weight loss, steatorrhea, and diarrhea; their annual incidence is 1 in 40 million [96–98]. Initial treatment in VIPomas and symptomatic somatostatinomas is based on fluid loss replacement and electrolyte correction. Octreotide and lanreotide may control symptoms in the majority of patients [96, 99, 100], but in refractory cases glucocorticoids may be used as adjuvant therapy [96]. Equivalent to other pancreatic NETs, molecular targeted therapy and PRRT may be useful in metastasized cases, but due to their low incidence, subgroup analyses on the efficacy of these novel therapeutic alternatives in these NETs are not available [13, 80–82, 101, 102].

2.6 Ectopic Hormone Production Syndromes

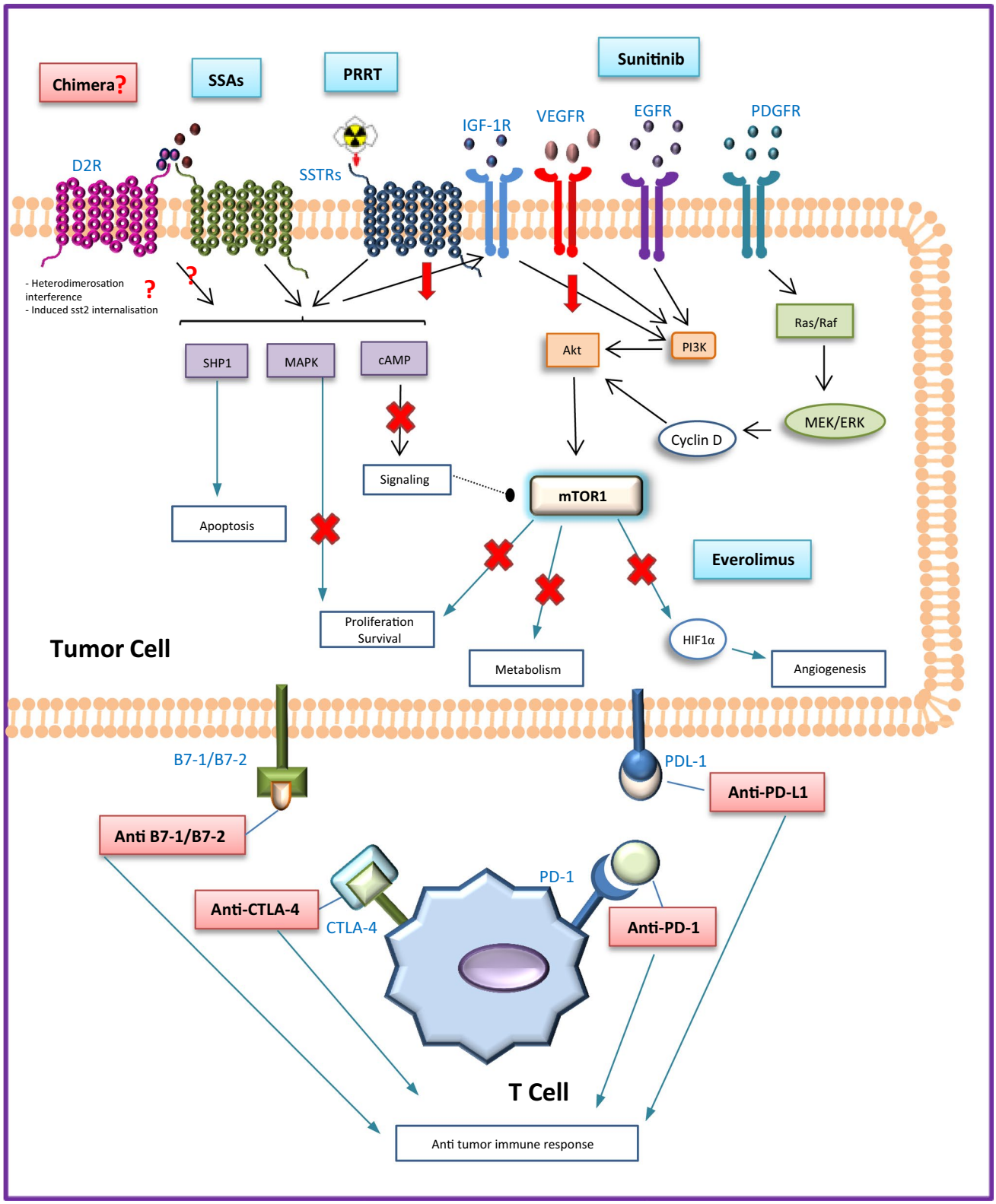
Ectopic hormone production is rare in NETs. Among them, adrenocorticotropic hormone (ACTH)-producing tumors are most commonly observed. Ectopic release of other peptides includes corticotropin-releasing hormone (CRH), growth hormone-releasing hormone (GHRH), antidiuretic hormone, parathyroid hormone-related peptide (PTHrP), and gonadotropins [103–105]. The aim of treatment of these patients includes symptomatic long-term control, tumor stabilization or reduction, and prolongation of (progression-free) survival [104].

2.6.1 Adrenocorticotropic Hormone (ACTH)

The ectopic ACTH syndrome (EAS) causes approximately 10% of all cases of Cushing syndrome [106, 107]; clinical evolution is usually faster and characterized by mineralocorticoid effects (hypertension, hypokalemia, and edema), thromboembolic disease, and opportunistic infections [108]. Curative surgery is the primary treatment option but is often not possible [106, 109]. EAS can result in a critical condition for which aggressive medical therapy or life-saving bilateral adrenalectomy is necessary [108]. Medical treatment options for EAS include: (1) Tumor-directed drugs including somatostatin analogs (octreotide, pasireotide) and dopamine agonists that decrease tumoral ACTH secretion [108, 110–113]. The identification of SSTR expression in the tumor using radiolabeled somatostatin analogs may also help to identify suitable patients who might benefit from PRRT [95, 110, 114]. In addition, the tyrosine kinase inhibitors vandetanib and sorafenib may have antisecretory effects in selected cases with EAS [115, 116]. (2) Steroid synthesis inhibitors, which directly suppress adrenal cortisol production. In this sense, a combination of ketoconazole, metyrapone, and mitotane was shown to be effective in critically ill patients with EAS [117]. Additionally, the anesthetic drug etomidate can also rapidly suppress cortisol levels in an ICU setting [118]. (3) Glucocorticoid receptor antagonists. Mifepristone has a short onset of action and was shown to reverse morbidity of EAS in several cases [119].

2.6.2 Growth Hormone-Releasing Hormone (GHRH)

Ectopic GHRH production is predominantly encountered in patients with lung carcinoids [120]. Although some patients have evident clinical features of increased GH production, GHRH-staining may be positive in asymptomatic NET patients [121]. SSAs are widely used for the treatment of acromegaly due to GH-secreting pituitary adenomas, but medical treatment of acromegaly due to ectopic GHRH secretion is less well explored [122]. SSAs (octreotide and lanreotide) lower ectopic tumoral production of GHRH with



a subsequent decrease in circulating GH and insulin-like growth factor-1 (IGF-1) levels [123, 124]. In some cases, tumor control and clinical improvement may be achieved, but circulating GHRH may continue to be elevated [125].

2.6.3 Parathyroid Hormone-Related Protein (PTHrp)

PTHrp production is predominantly associated with PNETs; overall survival in patients with PTHrp production is

◂**Fig. 2** Current and future medical options for tumor control in neuroendocrine tumors. Current therapeutic options are presented in blue, possible novel therapeutic options are presented in red. SSAs and PRRT: increase apoptosis by activating the protein tyrosine phosphatase SHP1; decrease cell proliferation and survival through the mitogen-activated protein kinase (MAPK) and cyclic adenosine monophosphate (cAMP); and inhibit the signaling of the insulin-like growth factor receptor type 1 (IGFR-1); additionally, PRRT produces DNA double strand breaks induced by β-irradiation, consequently leading to apoptosis. Sunitinib is a multikinase inhibitor that modulates the phosphoinositate-3-kinase/Akt pathway (it blocks the vascular endothelial growth factor receptors (VEGFR) 1-3, the platelet-derived growth factor receptors (PDGFR) α and β, and the epidermal growth factor receptor (EGFR)). Everolimus decreases tumor cell proliferation, metabolism, survival, and angiogenesis through the mammalian target of rapamycin complex-1. The indirect inhibition of mTOR through the phosphoinositate-3-kinase/Akt produced by the SSAs seems to increase sensitivity to mTOR inhibition. Multireceptor chimeras may bind SSTR and D2R, and may enhance the signaling of the cAMP and JNK pathways; induced SST2R internalization and SST2R/D2R heterodimerisation interference have also been hypothesized. The interaction between some receptors expressed on the surface of cytotoxic T-cells (PD-1, CTLA-4) with ligands expressed on the tumor cells (PDL-1, B7-1/B7-2) downregulates the immune response to tumor cells; novel drugs that target these specific immune checkpoints inhibit this interaction allowing the immune system to maximize an efficient antitumor response. *SSAs* somatostatin analogs, *PRRT* peptide receptor radionuclide therapy, *IGF-1R* insulin-growth factor receptor type 1, *VEGFR* vascular endothelial growth factor, *EGFR* epidermal growth factor receptor, *PDGFR* platelet-derived growth factor receptors, *mTOR* mammalian Target of Rapamycin, *CTL4* cytotoxic T-lymphocyte antigen-4, *PDL-1* Programmed death-ligand 1

significantly shorter compared to pNET patients with normocalcemia [104, 126]. In PTHrp-producing NETs, hypercalcemia needs to be controlled. Treatment options for hypercalcemia include intravenous isotonic saline (corrects volume depletion), bisphosphonates (interfere with the osteoclast-mediated bone resorption), and denosumab (reduces the formation, function, and survival of osteoclasts via the receptor activator of nuclear factor κB (RANK) pathway) [104, 127, 128]. SSAs may help to improve symptom control but might be insufficient in patients with tumor progression [88, 104]. Tumor stabilization with parallel calcium control has been described in three of five patients after receiving PRRT with ^{177}Lu-DOTATATE [104].

3 Control of Tumor Growth

According to the latest analysis of the SEER database, 27.4% of NETs have distant metastases at diagnosis and 20% have regional infiltration [6]. Survival in NETs is related to tumor localization, tumor load, and grading, and these factors should be considered when selecting the appropriate medical treatment. Current and promising novel medical options for tumor growth control in NETs are presented in Fig. 2. The landmark clinical trials proving efficacy of the current medical options for tumor growth control in NETs are depicted in Table 1. Additionally, some current clinical trials for tumor growth control in NETs are depicted in Table 2.

3.1 Somatostatin Analogs

The antiproliferative effect of SSAs mostly depends on SSTR tumor expression, although indirect antitumor effects have been described as well [129]. SSAs may inhibit the cell cycle and increase apoptosis, and indirect effects may include immuno-modulation, antiangiogenic effects, and growth factor inhibition [9, 12, 100]. Octreotide and lanreotide bind preferably to SSTR2, and pasireotide has high binding affinity to multiple SSTR, particularly SSTR5 (Fig. 1) [130]. Long-acting preparations of octreotide and lanreotide monthly are usually used for disease stabilization in NETs [9, 131]. The antiproliferative effect of SSAs in NETs was initially evaluated in the PROMID study [132]. In this phase IIIB study, 85 well-differentiated metastatic midgut NETs were included. Patients were randomized to receive placebo or octreotide-LAR 30 mg every 4 weeks. A difference of 8.3 months in tumor progression was observed after comparing the octreotide and the placebo groups. Stable disease after 6 months was observed in 66.7% of patients treated with octreotide-LAR compared to 37.2% in the placebo group [132]. Despite the initial good response to octreotide LAR, the results from the long-term survival analysis revealed that overall survival (OS) was not significantly different in the placebo and the octreotide groups [133]. Interestingly, patients with resected primary tumor and/or lower liver tumor load benefitted more from the initial administration of octreotide [132, 133].

Similar to the PROMID study, the CLARINET study revealed that lanreotide (120 mg every 28 days) increased PFS of patients with metastatic well- and moderate-differentiated GEP NETs when compared to placebo (PFS rate of 65.1% in the lanreotide group and 33% in the placebo group) [134]. Usually SSAs induce tumor stabilization, but in selected cases SSAs can cause tumor shrinkage, possibly due to their effects on the perfusion of liver metastases [135]. Representative images of tumor shrinkage in response to lanreotide are depicted in Fig. 3a. According to the current clinical guidelines, SSAs are indicated in grade 1 (G1) non-functional NETs after progression without previous treatment (watch and wait strategy), in G1 NETs with high tumor load, or in non-functional grade 2 (G2) NETs with SSTR expression [23]. Because G1 and G2 NETs can initially show a stable disease course without treatment, markers are needed that can identify those patients in whom early treatment should be evaluated versus those patients in whom a wait-and-see strategy should be considered initially.

Table 1 Clinical trials supporting the current systemic strategies for tumor growth control in NETs

Drug/study	Study characteristics	Outcome results/safety
Somatostatin analogs		
CLARINET [134]	Randomized, double-blind, placebo-controlled, multicenter study. Advanced, well-/moderately differentiated, non-functioning, SSTR positive NETs (pancreas, midgut, hindgut, or of unknown origin). Placebo ($n=103$) or 120 mg of lanreotide autogel once every 28 days ($n=101$) for 96 weeks	PFS was significantly increased at 24 months in the lanreotide group 65.1% (95% CI 54.0–74.1) compared to 33.0% (95% CI 23.0–43.3) in the placebo group. Differences in quality of life were not statistically different between the two groups. The most common treatment-related adverse event was diarrhea (26% of the lanreotide group vs. 9% in the placebo group); 8 serious adverse events were considered to be related to the study drug (7 for lanreotide and 1 for placebo)
PROMID [132, 133]	Randomized, double-blind, placebo-controlled, multicenter study. Treatment-naive patients (well-differentiated midgut NET or unknown origin believed to be of midgut origin). Placebo ($n=43$) or octreotide-LAR 30 mg intramuscularly monthly ($n=42$) until tumor progression or death	PFS was increased in the octreotide group (14.3 months; 95% CI 11.0–28.8 months) compared to 6.0 months (95% CI 3.7–9.4 months) in the placebo group. Both groups had comparable levels of quality of life. The long-term tumor-related overall survival was similar in both groups. The most common treatment-related adverse events were gastrointestinal (6 patients in the octreotide-LAR group; 5 patients receiving placebo). Five patients treated with octreotide-LAR discontinued the treatment
Radionuclide therapy		
NETTER-1[166]	Open-label, randomized, controlled, multicenter study. Well-differentiated, metastatic midgut NETs progressive on octreotide LAR 30 mg every 4 weeks received 7.4 GBq of ^{177} Lu-Dotatate every 8 weeks [(four intravenous infusions, plus best supportive care including octreotide LAR) ($n=116$)] or octreotide LAR 60 mg every 4 weeks ($n=113$)	PFS at month 20 was 65.2% (95% CI 50.0–76.8) in the ^{177}Lu-Dotatate group vs. 10.8% (95% CI 3.5–23.0) in the control group. HR for death with ^{177} Lu-Dotatate group vs. control, 0.40; $p=0.004$. OS data is pending. Seven patients receiving ^{177}Lu-Dotatate and 10 in the control group stopped their participation in the trial due to adverse events. Nausea and vomiting were the most frequent adverse events in the ^{177} Lu-Dotatate group (59% and 47%, respectively). Grade 3–4 adverse events were similar in the two groups, but grade 3 or 4 neutropenia, thrombocytopenia, and lymphopenia were reported in 1%, 2%, and 9% in the ^{177} Lu-Dotatate group, respectively. No renal toxicity was reported
mTOR inhibitors		
RADIANT-3 [81]	Open-label, randomized, placebo-controlled study. Advanced, progressive, low- or intermediate-grade PNETs. Everolimus 10 mg/day ($n=207$) or placebo ($n=203$)	PFS was 11.0 months in the everolimus group compared to 4.6 months in the placebo group (HR 0.35; 95% CI 0.27–0.45; $p<0.001$). A non-significant OS benefit of 6.3 months was observed. Stomatitis was the most common adverse event (64% in the everolimus group vs. 17% in the placebo group). Infections and pneumonitis occurred in 12% of the patients in the everolimus group; grade 3 or 4 drug-related adverse events included anemia, hyperglycemia, stomatitis, thrombocytopenia, diarrhea, hypophosphatemia, and neutropenia. One death was related to the use of everolimus
RADIANT-4 [187]	Open-label, randomized, placebo-controlled study. Advanced, progressive, well-differentiated, non-functional lung, gastrointestinal NETs. Everolimus 10 mg/day ($n=205$) or placebo ($n=97$)	Everolimus was associated with a 52% reduction of the risk of progression or tumor-related death (HR 0.48; 95% CI 0.35–0.67; $p<0.00001$). OS did not significantly improve in the everolimus group. Stomatitis was the most common adverse event (63% in the everolimus group vs. 19% in the placebo group). Grade 3 or 4 drug-related adverse events included anemia, stomatitis, diarrhea, fatigue, and infections. Non-infectious pneumonitis occurred in 16% of the everolimus group

Table 1 (continued)

Drug/study	Study characteristics	Outcome results/safety
Tyrosine kinase inhibitors		
SUN 1111 [80, 195]	Multinational, randomized, double-blind, placebo-controlled study. Advanced, well-differentiated PNETs. 37.5 mg sunitinib ($n=86$) or placebo ($n=85$)	PFS was 11.4 months in the sunitinib group compared to 5.5 months in the placebo group (HR 0.42; 95% CI 0.26–0.66; $p<0.001$). The objective response rate was higher in the sunitinib group (9.3% vs. 0%). OS non-significantly improved by 10 months. Dose-limiting toxicities included grade 3 fatigue, grade 3 hypertension, and grade 2 bullous skin toxicity, which were reversible

SSTR somatostatin receptor, *NETs* neuroendocrine tumors, *PFS* progression-free survival, *CI* confidence interval, *HR* hazard ratio, *PRRT* peptide-receptor radionuclide therapy, *OS* overall survival, *PNETs* pancreatic neuroendocrine tumors

In addition, increased doses of SSAs seem to exert an apoptotic effect, which is not achieved with the standard doses [136]. These effects have been described in patients showing disease progression under regularly dosed lanreotide and octreotide [35, 137]. Currently, the CLARINET FORTE study is evaluating the safety and antitumor effect of lanreotide 120 mg given every 14 days in patients with pancreatic or midgut NETs with progressive disease under the same dose used every 4 weeks for at least 6 months (NCT02651987).

Pasireotide has also been studied in NETs, in which pasireotide concentrations correlated with tumor shrinkage in a non-significant manner [138]. Other studies have reported predominantly disease stabilization (60%) in treatment-naïve patients with grade 1–2 NETs, but also partial response (4%) and disease progression (36%) have been described [139]. Additionally, pasireotide-LAR has been compared to octreotide-LAR in patients with metastatic NETs and carcinoid symptoms. In these patients, pasireotide tended to increase the tumor control rate after 6 months and was associated with a longer PFS [43]. In the prospective phase II LUNA study in advanced (unresectable or metastatic), progressive, well-differentiated carcinoid tumors of the lung or thymus, pasireotide LAR treatment resulted in an objective tumor response in 39% of patients [140]. In the randomized, open-label, phase II COOPERATE-2 study of everolimus in combination with pasireotide LAR or everolimus alone in advanced, well-differentiated, progressive pancreatic neuroendocrine tumors, the addition of pasireotide to everolimus was not associated with improvement in PFS compared with everolimus alone [46]. Further investigation to evaluate the applicability of pasireotide alone or in combination with other therapies is required.

SSAs are generally well tolerated; common adverse events include nausea, abdominal pain, headache, dizziness, fatigue, and back pain; hematopoietic complications and bile stones have been also described [141]. These events may begin shortly after the first administration of the drug and may decrease progressively over the subsequent weeks as treatment continues [88]. In the PROMID study five patients stopped treatment due to an adverse event. In the CLARINET study, 25 of 101 patients had serious adverse events but only three were related to the study treatment [134].

3.2 Interferon-Alpha

Interferon-alpha has antiproliferative, pro-apoptotic, cytotoxic/cytostatic, and immunomodulatory effects in NETs [142, 143]. It has been considered as a second-line therapeutic option in progressive NETs under SSAs [23, 144]. Several studies have failed to show a significant

Table 2 Registered clinical trials for tumor growth control medical therapies in NETs

Drug	Study characteristics	Primary outcome/ClinicalTrials.gov Identifier
Somatostatin analogs		
Lanreotide (CLARINET FORTE)	Open-label single-group clinical trial for evaluating the efficacy and safety of lanreotide 120 mg every 14 days in well-differentiated, metastatic or locally advanced, unresectable pancreatic or midgut NETs with radiological progression with lanreotide 120 mg every 28 days	PFS (102 weeks)/NCT02651987
^{177}Lu-DOTA0-Tyr3-Octreotate (NETTER-1)	Multi-center, randomized, phase III study comparing ^{177}Lu-DOTA0-Tyr3-Octreotate to Octreotide LAR in patients with inoperable, progressive, somatostatin receptor positive midgut carcinoid tumors	PFS, OS data is pending/NCT02651987
Kinase inhibitors		
Sulfatinib	Randomized, multicenter phase III study to evaluate the efficacy and safety of sulfatinib (angio-immunokinase inhibitor targeting VEGFR, FGFR1, and CSF-1R kinases) vs. placebo in advanced PNETs	PFS (7 months after the last patient enrolled)/ NCT02589821
Sulfatinib	Randomized, double-blind, multicenter phase III study to evaluate the efficacy and safety of sulfatinib vs. placebo in advanced PNETs	PFS (9 months after the last patient enrolled)/ NCT02588170
Radionuclide therapy		
^{177}Lu-PRRT vs. ^{177}Lu-PRRT plus capecitabine	Open-label phase II study to compare the efficacy of ^{177}Lu-PRRT vs. ^{177}Lu-PRRT plus capecitabine in SSTR and 18-FDG PET/CT positive, G1-G2-G3 GEP-NETs	PFS (72 months)/NCT02736448
^{177}Lu-Octreotate -CAPTEM vs. (i) CAPTEM and (ii) ^{177}Lu-Octreotate	Two parallel phase II randomized open-label trials of PRRT with ^{177}Lu-Octreotate and CAPTEM (i) vs. CAPTEM alone in the treatment of low to intermediate grade PNETs (ii) vs. ^{177}Lu-Octreotate alone in the treatment of low to intermediate grade midgut NETs	PFS (12 months in PNETs and 24 months in midgut NETs)/NCT02358356
^{177}Lu-edotreotide vs. Everolimus	Prospective, randomized, controlled, open-label, multicenter phase III study to evaluate the efficacy and safety of PRRT with ^{177}Lu-edotreotide compared to everolimus in GEP-NETs	PFS assessed up to 24 months/NCT03049189
^{177}Lu-DOTA0-Tyr3-Octreotate vs. sunitinib	Open-label randomized phase II antitumor efficacy of PRRT with ^{177}Lu-DOTA0-Tyr3-Octreotate vs. sunitinib in unresectable progressive well-differentiated PNETs	PFS (12 months)/NCT02230176
mTOR inhibitors		
Everolimus and LEE011 (Ribociclib)	Open-label study to evaluate the efficacy and safety of the combination LEE011 (inhibitor of cyclin D1/CDK4 and CDK6 pathway) 300 mg once daily for 3 weeks (4th week off) and everolimus 2.5 mg daily in foregut WDNETs	PFS (2 years)/NCT03070301
Everolimus and TMZ	Open-label study to evaluate everolimus and temozolomide as first-line treatment in advanced NEC with a Ki67 of 20–55%	Disease control rate/NCT02248012
Everolimus and bevacizumab	Randomized phase II study of everolimus alone vs. combined with bevacizumab in patients with PNETs (currently active, not recruiting)	PFS (up to 3 years)/NCT01229943
Everolimus and cisplatinum	Open-label phase II study of cisplatinum and everolimus in metastatic or unresectable NEC of extrapulmonary origin	Disease control rate/NCT02695459

Table 2 (continued)

Drug	Study characteristics	Primary outcome/ClinicalTrials.gov Identifier
Immunotherapy		
Pembrolizumab	Open-label phase II study of monotherapy with pembrolizumab (humanized anti-PD-1 monoclonal antibody) in patients with metastatic high-grade NETs who have failed platinum-based chemotherapy	Objective response rate/NCT02939651
PDR001	Open-label phase II study to evaluate PDR001 (high-affinity, ligand-blocking, humanized IgG4 antibody directed against PD-1) in advanced or metastatic, well-differentiated, non-functional, thoracic and GEP-NETs or GEP-NECs	Overall response rate/NCT02955069
Durvalumab and tremelimumab	Multicenter open-label phase II study to evaluate the combination therapy between durvalumab (MEDI4736; humanized antibody against PD-1) and tremelimumab (CTLA-4 inhibitor) in advanced/metastatic, grade 1/2 (G1/G2) lung and GEP-NETs, and grade 3 (G3) GEP- tumors or of unknown primary site after progression to previous therapies	Clinical benefit rate/NCT03095274

NETs neuroendocrine tumors, *PRRT* peptide receptor radionuclide therapy, *CAPTEM* Capecitabine/temozolomide, *PFS* progression-free survival, *OS* overall survival, *VEGFR* vascular endothelial growth factor, *FGFR* fibroblast growth factor receptor, *CSF-1R* colony-stimulating factor 1 receptor, *PNETs* pancreatic neuroendocrine tumors, *PRRT* peptide receptor radionuclide therapy, *18-FDG PET/CT*18-fluorodeoxiglucose positron emission tomography–computed tomography, *GEP-NET* gastroenteropancreatic neuroendocrine tumors, *CDK* cyclin-dependent kinases, *WDNETs* well-differentiated neuroendocrine tumors, *TMZ* temozolomide, *NEC* neuroendocrine carcinoma, *PDGFR* platelet-derived growth factor receptor, *PD1* programmed death-1, *CTLA-4* cytotoxic T-lymphocyte-associated protein 4

additional effect of interferon-alpha on top of that of SSAs [32, 44, 145]. Tumor response rates of about 10% have been reported [146] and its efficacy is similar to other agents including bevacizumab when combined with SSAs [147]. Unfortunately, several adverse effects have been described; a pegylated formulation seems to be associated with decreased side effects, and its combination with octreotide seems to be better tolerated [146, 148]. Despite this, the availability of novel therapeutic options with higher efficacy and lower side effects limit the applicability of this drug for tumor control [149].

3.3 Peptide Receptor Radionuclide Therapy (PRRT)

PRRT with a somatostatin analog allows targeted delivery of radionuclides to tumor cells expressing high levels of SSTR. Radiolabeled SSAs consist of a radionuclide isotope (^{90}Y or ^{177}Lu), a carrier molecule (generally octreotide or octreotate), and a chelator (usually DOTA: tetra-azacyclododecane-tetra-acetic acid or DTPA: diethylenetriamine pentaacetic acid) [150]. ^{177}Lu-DOTA-octreotate or ^{177}Lu-Dotatate is the most studied molecule. The ^{177}Lu radionuclide is characterized by the emission of β-rays, which have an intermediate tissue penetration, and γ-rays, which are used for monitoring and dosimetry by post-therapy scintigraphy [151].

Treatment response is directly related to the expression of SSTR in the tumor, making it a predictive marker of response [152], although tissue SSTR immunohistochemistry has no additional value to SSTR scintigraphy in predicting tumor response to PRRT [153]. For PRRT, patients should have a positive NET histology and a positive SSTR scintigraphy with ^{111}In-DTPA-octreotide (OctreoScan; lesion uptake equal or greater than the liver uptake) or a positive ^{68}Ga-DOTA-SSA PET-CT [154]. In 443 bronchial and GEP NET patients PRRT induced an objective tumor response (complete or partial) in 39% and stable disease in 43% of patients. In this cohort PFS was 29 months (range 26–33) and OS 63 months (range 55–72) [155]. Tumor response may differ according to the primary tumor localization and tumor load [156]. OS is also different in NETs of different localizations (pancreas 71 months (95% CI 56–86), midgut 60 months (95% CI 52–68))[155]. In contrast, response rates are lower in patients with larger tumor load and higher liver infiltration [157]. A representative example of tumor response to PRRT is depicted in Fig. 3b.

An OS of 27–95 months and a PFS of 16–29 months have been reported in NET patients receiving treatment with ^{90}Y-DOTATOC [158–160], but regimens employing

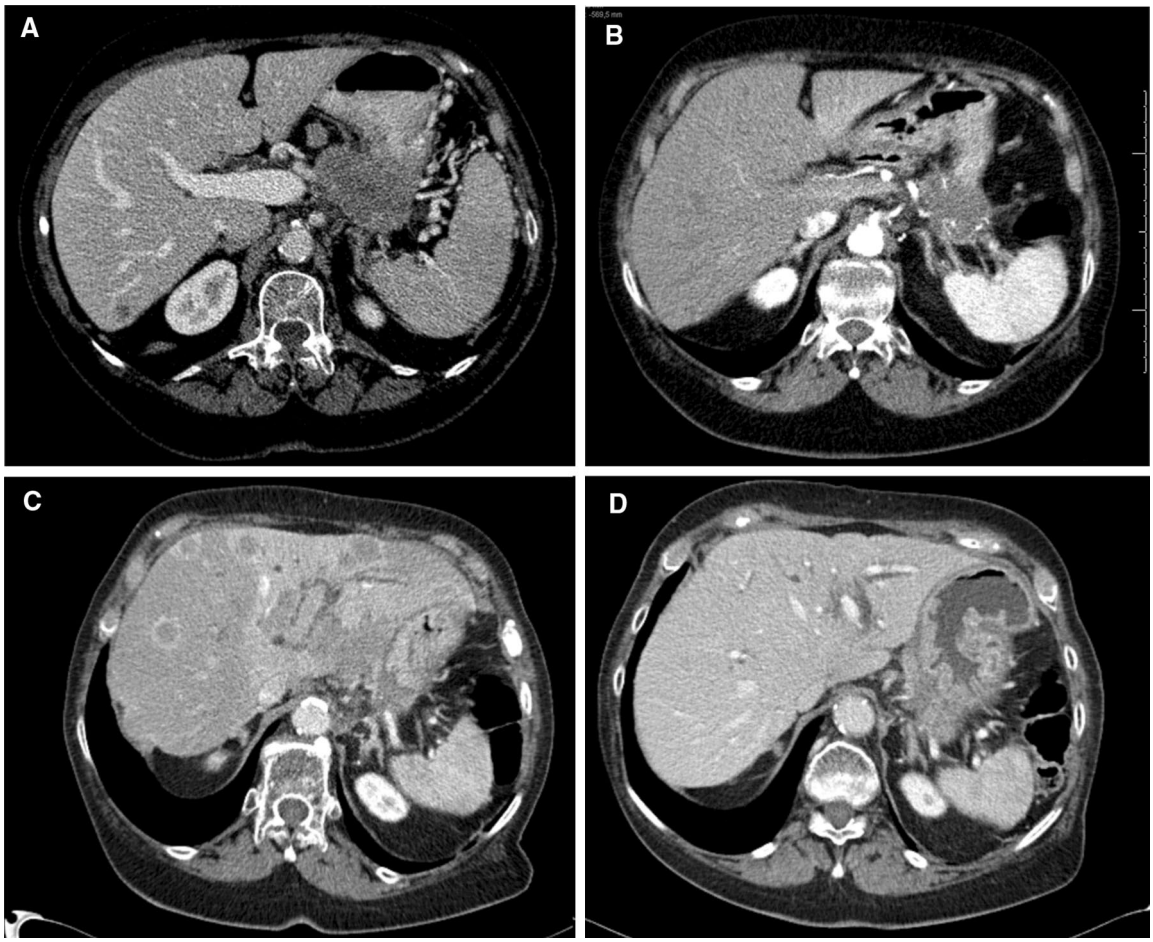


Fig. 3 Peptide receptor radionuclide therapy in neuroendocrine tumors (NETs). **a** CT imaging of a pancreas neuroendocrine tumor grade 2 with lymphatic and liver metastasis (segment 6); in this case, four cycles of peptide receptor radionuclide therapy (cumulative dose 30 Gbq) was administered resulting in decreased size of the primary tumor (**b**). After 6 years of partial response and stable disease, the primary tumor increased in size accompanied by new liver and mesenteric metastasis (**c**). Because of an initial good treatment response, two cycles of PRRT (14.9 GBq) were administered, and a decreased size of primary tumor and liver metastasis were observed (**d**). Images are of an NET patient evaluated in the ENETS Center of Excellence Erasmus MC, Rotterdam. Informed consent was provided

^{90}Y have been associated with an increased incidence of renal toxicity. Available studies are difficult to compare since the inclusion criteria and basal characteristics of the included patients differ considerably [150]. Single-center studies evaluating ^{177}Lu-Dotatate reported a median OS of 46 months, median time to progression of 36–40 months, and PFS of 33–36 months [82, 161–163]. Imaging response rates of 18–44% (by RECIST criteria) and improvement in quality of life have also been reported [164, 165]. The pivotal phase III NETTER-1 trial for the first time evaluated the efficacy of PRRT with ^{177}Lu-DOTATATE in a multicenter, randomized clinical trial. This study included 229 patients with well-differentiated, metastatic midgut NETs that were progressive on a standard dose of long-acting SSA. Patients were randomized to receive four cycles of PRRT with ^{177}Lu-Dotatate or a double dose (60 mg/28 days) of octreotide LAR. The primary outcome was an increase in PFS (median not reached vs. 8.4 months) in favor of patients treated with PRRT. This study also reported a 79% reduction in the risk of progression or death compared to octreotide and increased overall response rate (ORR) in the PRRT group (18%) compared to 3% in the control group [166]. Despite PRRT being a promising treatment in GEP-NETs, the application in lung NETs may be limited due to a low expression of SSTR in some cases, especially in some atypical lung carcinoids; notwithstanding, ORR of 15%, disease stabilization of 47%, and OS of 52 months (95% CI 49–55) have been reported [155, 167].

In the case of tumor progression after an initial good response, retreatment with PRRT represents an alternative. In this sense, disease control rates of 70–85% have been reported, but tumor response is limited [168, 169]. ^{177}Lu-DOTATATE has also been evaluated with radiosensitizing agents; its use in combination with 5-fluorouracil,

capecitabine, or temozolomide may increase the response rate (ORR 24–38%), but toxicity should still be evaluated [170–172]. Similar ORR has been reported when combined with everolimus [173]. Some case reports and series have suggested the use of pre-operative PRRT for downstaging NETs [174–176], but further investigation is still required on the efficacy of neoadjuvant PRRT in patients with initially unresectable NETs.

PRRT is generally well tolerated. Nausea, fatigue, or abdominal pain may occur; they have been related to the amino acid infusion given for kidney protection and are self-limiting within 24 h [150]. Other adverse effects include neutropenia (1%), thrombocytopenia (2%), and lymphopenia (9%) [166]. Increased serum levels of liver enzymes and chromogranin A during or directly after therapy may be related to radiation-induced inflammation or progressive disease, and follow-up and repeated measurements are required [177]. Long-term side effects of PRRT may include renal failure and acute leukemia or myelodysplastic syndrome in 1–2% of cases [150, 155, 156]. Some clinical conditions increase PRRT toxicity (hypertension, diabetes, and renal or bone marrow impairment).

Currently several clinical trials aim to further optimize PRRT by evaluating the efficacy of PRRT alone or in combination with chemotherapeutic agents (capecitabine or capecitabine/temozolomide) in patients with undifferentiated NETs (NCT02358356). Novel radioligands include SSTR antagonists, the combination of PRRT with immunotherapy, and the use of α emitters [150]. SSTR antagonists may have higher tumor uptake, longer retention, and decreased radioactivity in healthy organs compared to ^{177}Lu-Dotatate [150, 178]. Alpha emitters, such as ^{213}Bi, can induce more DNA damage; however, toxicity is a problem for alpha-emitting radionuclides, which limits their applicability in the clinical practice. Additionally, other pharmaceutical agents (olaparib) could sensitize NET cells to PRRT according to in vitro models [179]. Predictive response models are also under study. For instance, NET blood gene expression assays have been evaluated in recent years [180]; these results, in combination with tumor grade, may help to predict the response to PRRT [181]. Recently a binary predictive quotient was described based on the use of NET blood gene transcripts combined with Ki67, and this quotient predicted 100% of responders and 84% of non-responders with an accuracy of 95% [182]. These data should, however, be validated in independent cohorts. Soon the results of the COMPETE study will be available. The aim of this multicenter phase III study is to evaluate the efficacy and safety of PRRT (^{177}Lu-Edotreotide), compared to everolimus, in progressive GEP-NETs with positive expression of SSTR (NCT03049189). This comparison aims to provide information on the treatment sequence that should be followed in progressive NETs under SSAs. Finally, the development of new radiopeptides targeting other receptors (e.g., gastrin-releasing peptide) may also represent a therapeutic option in the future [183].

3.4 Everolimus

The mTOR pathway plays an important role in the regulation of cell proliferation in NETs [15]. The efficacy of the PI3 K/AKT/mTOR inhibitor everolimus in well-differentiated NETs has been shown in several clinical trials [23]. In the phase III RADIANT 3 trial, everolimus was compared to placebo in patients with low or intermediate-grade PNETs with radiologic progression within the previous year. PFS was longer in the everolimus group. Additionally, only a non-significant 6.3 months OS benefit was observed, and this last result may be related to the switch of patients from the placebo group (85% experienced progressive disease) to the open-label everolimus group [184]. Despite this, the effect of everolimus on PFS and OS was independent of the prior use of chemotherapy or SSAs [184–186]. A similar study was conducted in gastrointestinal and lung NETs (RADIANT 4), where increased PFS (11 vs. 3.9 months) and higher disease control rate (81% vs. 64%) in favor of the everolimus-treated group were reported [187]. However, although everolimus is considered a safe drug, treatment can be accompanied by grade 3 and 4 drug-related adverse events (diarrhea, infections, anemia, fatigue, hyperglycemia) [187], which may limit treatment tolerance and consequently patient adherence. Importantly, the RADIANT 4 study, as the previous ones, failed to demonstrate statistically significant improvements in OS [187], which should be taken into account especially in those patients with poor treatment tolerance.

The combination of everolimus and octreotide LAR has also been compared to octreotide LAR alone in functioning GEP- and lung NETs (carcinoid syndrome; phase III RADIANT 2). PFS was 5.1 months longer in the combination group but the hazard ratio (HR) was not statistically significant between the two groups [188]. In lung NETs, 2.4-fold longer PFS, 28% reduction in the risk of disease progression, and a twofold increase in the proportion of patients with tumor shrinkage were reported in the combination arm [189]. In colorectal NETs similar results have been described, including a fourfold prolonged PFS and increased frequency of tumor shrinkage (67% vs. 37%) [190]. As opposed to the positive results of combination therapy with everolimus and octreotide LAR, the combination of everolimus with pasireotide did not improve PFS or OS when compared to everolimus alone in progressive PNETs [46]. In contrast, in lung and thymic NETs the combination of pasireotide (60 mg every 28 days) with everolimus increased the progression-free rate (58.5%) when compared to pasireotide (39%) or everolimus (33.3%) at 9 months (phase II LUNA trial). Importantly, 27% of patients discontinued the

treatment due to progressive disease or adverse events [191]. A synergistic effect of epidermal growth factor receptor (EGFR) and mTOR pathways inhibitors has been suggested in bronchial carcinoids [192]. For this reason the combination with sunitinib/erlonitib is currently under study.

Everolimus is considered as first-line therapy in progressive atypical lung carcinoids, SSTR-negative lung NETs, and in well-differentiated midgut SSTR-negative NETs [23]. Currently several studies are evaluating the combination of everolimus with other therapies including chemotherapeutic agents, SSAs, molecular targeted therapies, radiotherapy, and PRRT.

3.5 Sunitinib

Because NETs are generally hypervascularized tumors, treatment with antiangiogenic drugs seems a rational approach. Sunitinib is as an oral multi-targeted tyrosine kinase inhibitor (TKI) that inhibits multiple angiogenic factors including the vascular endothelial growth factor receptors 1-3 (VEGFR), the stem-cell factor [SCF] receptor, and the platelet-derived growth factor receptors [193]. Initially in a two-cohort phase II study, sunitinib, administered 50 mg/day orally for 4 weeks followed by 2 weeks off treatment, reported poor response rates in PNETs and carcinoids (16.7% and 2.4%, respectively) [194]. In contrast, a placebo-controlled phase III study in progressive PNETs (SUN 1111 trial) reported increased PFS in the sunitinib group (11.4 months, hazard ratio for progression or death, 0.42; 95% CI 0.26–0.66) compared to placebo (5.5 months), and resulted in study discontinuation due to a higher incidence of adverse events and deaths in the placebo group [80]. Recently a retrospective imaging analysis of 171 patients with well-differentiated metastatic and/or progressive PNETs was performed. Patients received 37.5 mg sunitinib daily or placebo. PFS was increased in the sunitinib group (12.6 months) compared to placebo (5.8 months). 5 years after the study closure, median OS was 38.6 (25.6–56.4) months for sunitinib and 29.1 (16.4–36.8) months for placebo (HR, 0.73; 95% CI 0.50–1.06; $p = 0.094$). In this study 69% of patients randomized for placebo crossed over to sunitinib, probably affecting the significance of the OS [195], as has been reported in previous studies [196]. As for everolimus, significant improvement in OS has not been reported yet.

Sunitinib is associated with several adverse events including hypertension, diarrhea, nausea, vomiting, asthenia, skin toxicity, and fatigue [80]. Importantly, drug-related adverse events with sunitinib are increased threefold as compared with placebo [193], but fewer grade 3–4 toxicities are observed when compared with chemotherapeutic agents [197]. Dose reduction or temporary interruption of therapy may resolve the adverse clinical situation [193]. Importantly, no differences in the quality-of-life index have been reported when compared to placebo [193].

Sunitinib dose reduction should be considered when co-administered with strong CYP3A4 inhibitors, including ketoconazole, ritonavir, itraconazole, erythromycin, or clarithromycin. In contrast, dose should be increased when administered with CYP3A4 inducers, such as dexamethasone, phenytoin, carbamazepine, or phenobarbital [193].

Sunitinib is currently being compared to other treatment options in NETs including everolimus and PRRT. Current therapeutic options and a possible therapeutic sequence are depicted in Fig. 4.

3.6 Other Treatments

Other TKIs and antiangiogenic drugs have been evaluated in NET patients in open-label phase II studies (Table 2). Importantly, these therapies have been considered as promising options in NETs, but further studies are still required. In this sense, despite promising phase II data of bevacizumab administration in patients with gastrointestinal NETs, a phase III trial failed to show superior efficacy of bevacizumab compared to interferon alfa-2b [147]. The combination therapy of sorafenib and bevacizumab can induce antitumoral response, but was accompanied by an unfavorable safety outcome in a phase II study [198]. In contrast, the combination of bevacizumab with everolimus showed improved tumor response rates but no significant effect on PFS [199]; even more, the combination of everolimus with sorafenib reported dose-limiting toxicities [200]. Biochemical and radiological response has been described in PNETs treated with pazopanib [201], but further evaluation is still required; importantly, results of randomized trials are still pending and its combination with temozolomide is currently under evaluation (NCT01465659).

Systemic chemotherapy is indicated for the poorly differentiated grade 3 neuroendocrine carcinomas. Chemotherapy is not discussed in this review, but some publications describe the significant advances in this field in the last years [16, 202–204].

4 Future Directions

The comprehensive evaluation of signaling pathways regulating cell proliferation involved in NET development and progression has opened new perspectives for the medical treatment of these tumors. Current clinical trials for tumor growth control including novel drugs, treatment comparisons, and combinations are summarized in Table 2.

mTOR inhibitors and TKIs are the most representative examples, but other novel pathway-directed therapeutic

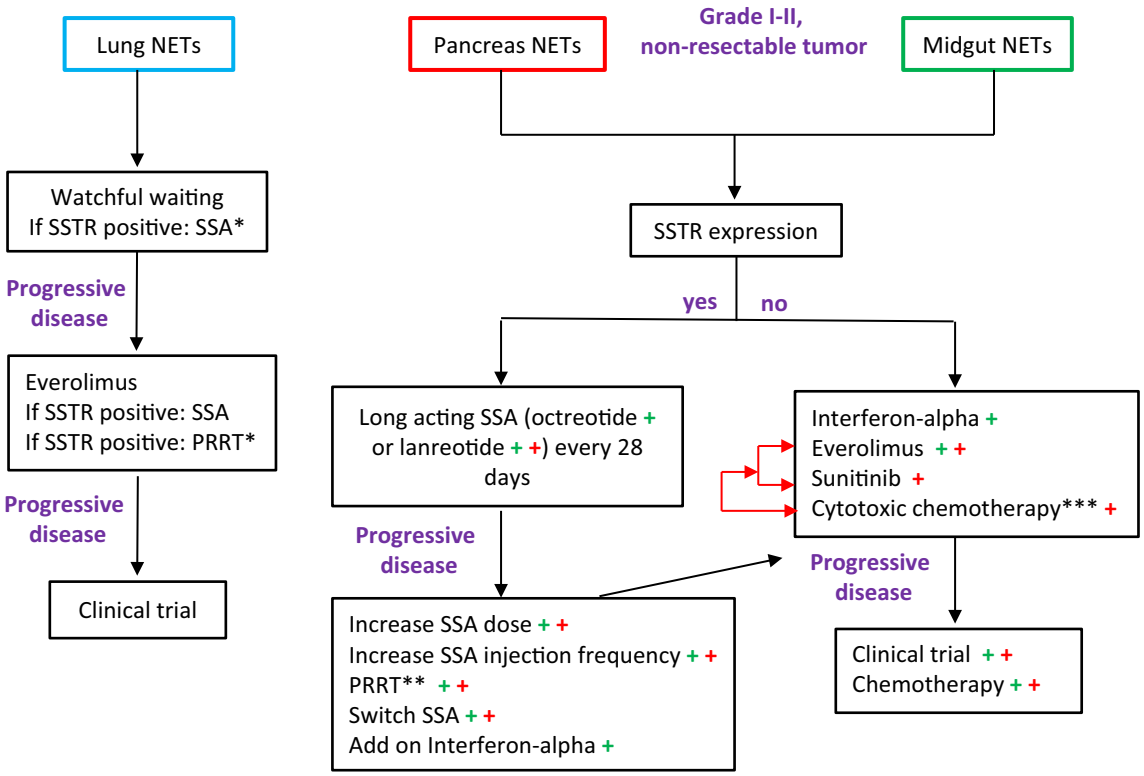


Fig. 4 Treatment algorithms for tumor control in neuroendocrine tumors (NETs). Summary of current medical strategies for tumor control in NETs according to the primary tumor site. Legend: Blue, red and green colors represent lung, pancreas and midgut NETs respectively. *SSTR* somatostatin receptor expression, *SSA* somatostatin analog, *PRRT* peptide receptor radionuclide therapy. *Not registered for this indication, **PRRT has been approved in Europe for midgut NETs and in the USA for midgut and pancreatic NETs, ***streptozocin/5-fluorouracil or streptozocin/doxorubicin; temozolomide/capecitabine as an alternative regimen

compounds are also currently being evaluated in (pre-)clinical studies [205]. Current clinical trials include head-to-head comparisons between novel therapies (PRRT vs. everolimus/sunitinib/capecitabine-temozolomide) and combination therapies (everolimus with bevacizumab/cisplatinum/temozolomide; PRRT with capecitabine-temozolomide). Additionally, trials that compare treatment sequences are also recruiting patients (sequencing of streptozocin-5-FU followed by everolimus vs. the reverse order of treatment, NCT02246127). These results may help to improve the sequence of therapy in NET patients.

Other examples of potential new treatment options include immunotherapy and somatostatin-dopamine multi-receptor chimeras. The mechanisms of action of immune checkpoint inhibitors and multi-receptor chimeras are also depicted in Fig. 2.

Immune checkpoint inhibitors have rapidly advanced and improved the management of several tumors in the last years [206, 207]. Programmed death-ligand 1 (PD-L1) is expressed on several cancer cells and interacts with PD1, which is expressed on T cells. This ligand-receptor interaction inhibits T cells and blocks their antitumor immune response [208, 209]. PD1/PDL1 expression has been demonstrated in several cancers [210–212]. Studies testing anti-PD-L1 or anti-PD1 agents have shown promising results in, for instance, small-cell lung cancer (SCLC) and melanoma [209]. The expression of PD-L1 was demonstrated in GEP- and lung (large cell neuroendocrine carcinoma) NETs using immunohistochemistry and qPCR [208, 213, 214]. Additionally, an inverse relation between PD-L1 and angiogenesis/hypoxia factors (vascular endotelial growth factor-A, hypoxia inducible factor 1a) has been described [215]. Importantly, PD-L1 has been associated with clinical variables in lung and GEP-NETs, including histological type, tumor grade, and survival [208, 216], which have not been described in midgut NETs [214]. Observations that the expression levels of PD-1 and PD-L1 were an independent survival prognostic factor in NETs [216] should be subjected to further study [214].

The use of cytotoxic T-lymphocyte antigen-4 (CTL4) blockers has also been reported in SCLC [217]. CTL4 is a critical negative regulator of the antitumor T-cell response, and its inhibition has encouraging effects in SCLC and melanoma [217, 218]. Additionally, the efficacy of immune checkpoint inhibitors may be affected by the presence of tumor infiltrating lymphocytes (TILs) [219]. TILs have been

suggested as a survival predictor for intermediate grade (Ki 67 2–20%) PNETs, since increased recurrence-free survival was observed in patients with higher TIL density [219]. The modulation of TILs density may also be a promising therapeutic option in the future. Despite immunotherapy having an important role in the management of other types of cancer, the effect on well-differentiated NETs according to preliminary data seems to be limited, although it may represent an option for G3NETs/NECs, which needs further investigation [220].

Multi-receptor interaction has been suggested as an efficacious and selective therapeutic strategy for enhancing the effects of somatostatin [221]. The presence of hetero-dimers has been described among SSTRs and between SSTRs and other receptor families, including dopamine receptors, especially the dopamine receptor subtype 2 (D2R) [222, 223]. Based on this, some structural chimeric molecules that combine elements of SSAs and dopamine analogs (DA) have been developed [221]. In vitro studies using a pancreatic NET cell model revealed inhibitory properties of chimeras on hormone secretion without affecting cell proliferation [224]. Importantly, BIM-23A760, a chimeric compound that activates SSTR2 and D2R, acutely decreased growth hormone and prolactin secretion in pituitary tumors, but long-term effects disappeared due to a dopaminergic metabolite that may interfere with the activity of the parent molecule [221]. An open-label, multicenter clinical trial in patients with carcinoid syndrome was started for evaluating the efficacy of BIM-23A760. Unfortunately, this study was prematurely terminated and primary/secondary outcomes were not analyzed (NCT01018953). Currently research is focused on the improvement of chimeric molecules that could keep a long-term effect.

5 Conclusions

The number of systemic treatment options for NETs aiming to control either hormone production and/or tumor growth has significantly increased and improved in the last years. A higher number of clinical trials and approved therapeutic agents have further facilitated the management of NET patients. SSAs were found to have antiproliferative effects, next to their inhibitory action on hormone secretion, and can induce sustained stabilization in grade 1–2 NETs. If progression occurs under SSAs therapy, PRRT seems to be the most rational second-line treatment, considering its efficacy and side effects, with everolimus and sunitinib (for PNET) as the next options. To further improve PFS and hopefully OS, further randomized studies are needed to establish the optimal role, sequence, and/or combination(s) of the currently available and emerging treatment options. In addition, future studies should further characterize (epi)genetic aspects and regulatory pathways of NETs to identify new targets for medical therapy.

Compliance with Ethical Standards

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