Current treatments and future potential of surufatinib in neuroendocrine tumors (NETs)

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***Abstract*:** Neuroendocrine tumors (NETs) are rare, heterogeneous, often indolent tumors that predominantly originate in the lungs and gastrointestinal tract. An understanding of the biology and tumor microenvironment of NETs has led to the development of molecularly targeted treatment options including somatostatin analogs, tyrosine kinase inhibitors, mammalian target of rapamycin inhibitors and peptide receptor radionuclide therapy. Although increases in progression-free survival have been demonstrated, most currently approved NET therapies are limited by the development of tumor resistance. Surufatinib (HMPL-012, previously known as sulfatinib) is a new, oral, small-molecule tyrosine kinase inhibitor that potently inhibits vascular endothelial growth-factor receptor 1–3, fibroblast growth-factor receptor 1, and colony-stimulating-factor-1 receptor. This unique combination of molecular activities inhibits tumor angiogenesis, regulates tumor-immune evasion, and may decrease tumor resistance. Surufatinib demonstrated statistically significant, clinically meaningful antitumor activity, including tumor shrinkage, in two phase III studies recently completed in China in advanced pancreatic NETs and advanced extrapancreatic NETs. The safety profile of surufatinib in neuroendocrine tumors studies was consistent with previous surufatinib clinical studies. In an ongoing study in United States (US) patients with NETs of pancreatic origin and NETs of extrapancreatic origin previously treated with everolimus or sunitinib, surufatinib has also demonstrated promising efficacy. Furthermore, the pharmacokinetic and safety profile of surufatinib in US patients is similar to data collected in studies done in China. These positive phase III results support the efficacy of surufatinib in patients with advanced, progressive, well-differentiated NETs regardless of tumor origin.

Keywords: neuroendocrine tumor, tumor microenvironment, tyrosine kinase inhibitor, blood-based biomarker

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Introduction

Neuroendocrine tumors (NETs) are rare, heterogeneous, often indolent tumors that predominantly originate in the lungs and gastrointestinal (GI) tract but can also originate in other organs, or be of unknown origin.[1] While rare, the incidence of NETs has been steadily increasing over the past 5 decades.[2–4] Poorly differentiated NETs are neuroendocrine carcinomas. Well-differentiated NETs are classified into three histologic categories based on the World Health Organization (WHO) 2019 classification.[5] Grade 1 (G1) NETs are well-differentiated, low-grade tumors that are more indolent and have a mitotic rate (mitoses/2 mm^2) of <2 and a Ki-67 index of $<3\%$. Grade 2 (G2) NETs are well-differentiated, intermediate-grade tumors with a mitotic rate of 2–20 and a Ki-67 index of 3–20%. Grade 3 (G3) NETs are well-differentiated, high-grade, more aggressive tumors with a mitotic rate of >20 and a Ki-67 index of $>20\%$. NETs can also be classified based on hormonal secretion. Functional NETs, in contrast to nonfunctional NETs, can produce peptide hormones and vasoactive substances, including serotonin.[6] These functional, secretory NETs can cause carcinoid syndrome

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that results in diarrhea, flushing, and heart valve issues due to chronic elevation of serotonin levels.[7]

An understanding of the biology and tumor microenvironment of NETs has led to the development of molecularly targeted treatment options. For example, some NETs are characterized by high expression of somatostatin receptors.[8] Somatostatin receptor signaling regulates the proliferation of these tumors and the characteristic hormone production of functional NETs.[6] Therefore, somatostatin analogs (SSAs) have been developed to treat these symptoms. Similarly, the phosphatidylinositol-3-kinase (PI3K)/protein kinase B (Akt) and mammalian target of rapamycin (mTOR) pathway are overexpressed in NETs. mTOR is shown to be involved in NET progression through actions on proliferation, angiogenesis and metabolism.[8] Mutations in the mTOR pathway have also been found in NETs of pancreatic origin (pNETs), spurring the development of inhibitors of this pathway as a treatment option for NETs.[9]

NETs are among the most heavily vascularized tumors, and express many pro-angiogenic molecules, including vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and platelet-derived growth factor (PDGF).[8] This knowledge has led to the development of antiangiogenic VEGF inhibitors to treat NETs.

Another hallmark of NETs is their ability to evade the immune system, which contributes to tumor progression. Immune cell infiltration, including tumor-associated macrophages (TAMs), is shown to be involved in immune evasion and tumor development and progression.[10] Colony-stimulating-factor 1 (CSF-1) promotes macrophage recruitment to the tumor microenvironment and activation of TAMs.[10] In one study, when a mouse model of pancreatic islet cancer was crossed with a CSF-1-deficient mouse, there was a decrease in tumor burden, and TAM levels were decreased by 50% in the pNETs that did develop.[10] Adaptation of tumors to VEGF inhibition may be mediated by macrophage recruitment *via* overexpression and deposition of the matrix protein periostin, and therefore, the authors of this study encouraged clinical testing of molecules that inhibit both VEGF receptor (VEGFR) and CSF-1 receptor (CSF-1R).[11]

Upregulation of programmed cell-death receptor 1 (PD-1) and programmed cell-death ligand (PD-L1) has also been implicated as another mechanism of local tumor-immune evasion.[12] PD-1 overexpression decreases the antitumor activity of T cells. This local immune suppression in NETs, through infiltration of TAMs or upregulation of PD-1 on T cells, can contribute to tumor progression and is an independent predictor of poor prognosis.[13] Development of PD-1 inhibitors is designed to promote activation of cytotoxic T cells to attack tumors.[12] Combination therapies that enhance tumor susceptibility to immune-checkpoint inhibitors are currently being studied; however, current data have been disappointing in well-differentiated NETs.[14]

There is a clear unmet medical need for effective treatment options for NETs, given the increasing incidence, poor prognosis, and advanced stage at diagnosis. In addition, studies are needed to determine the optimal sequence of current therapies and the impact of combinations of therapies on efficacy and safety. In this review, we will discuss current therapies for NETs, their mechanism of action and limitations, based on knowledge of the biology and microenvironment of the tumor. Finally, we will introduce surufatinib, a new treatment with multiple mechanisms of action that targets both tumor angiogenesis and immune system evasion.

Current therapies

Surgery is the best choice for NETs if diagnosed early. For metastatic or unresectable NETs, beside locoregional therapies, debulking surgery, and potentially liver transplantation,[15] there are several systemic treatment options including SSAs that modulate hormone and growth-factor release, tyrosine kinase inhibitors with antiangiogenic properties, inhibitors of the PI3K/Akt and mTOR signaling pathway that is implicated in unregulated cell growth in NETs, peptide receptor radionuclide therapy (PRRT), and cytotoxic agents (Table 1). Newer therapies, which are being tested for treatment of NETs, include cytotoxic chemotherapy agents and inhibitors of PD-1 and its ligand.[16,17]

Somatostatin analogs: octreotide and lanreotide

High-affinity SSAs, with increased half-life compared with somatostatin, bind to somatostatin receptors expressed by NETs and suppress the secretion of hormones and growth factors by these tumors.[18] Expression of somatostatin

Table 1. Current therapies for treatment of NETs.

Drug class	Drug	Target	Mechanism of action	Route of administration
SSAs				
	Octreotide	Somatostatin receptors 2, 5	Antisecretory, antiproliferative	Intramuscular, subcutaneous injection
	Lanreotide	Somatostatin receptors 2, 5	Antisecretory, antiproliferative	Subcutaneous injection
Tyrosine kinase inhibitors				
	Sunitinib	VEGFR 1–3 inhibition	Antiangiogenic, antiproliferative	Oral
mTOR inhibitors				
	Everolimus	PI3K/AKT, mTOR inhibition	Antiangiogenic, antiproliferative	Oral
PRRT				
	^{177}Lu-DOTATATE	Somatostatin receptors	Targeted delivery of radionuclides to tumor cells	Infusion
Chemotherapeutics				
	Streptozotocin	Alkylating agent	Cytotoxic	Infusion
	Temozolomide	Alkylating agent	Cytotoxic	Infusion
	Capecitabine	Antimetabolite	Cytotoxic	Infusion

^{177}Lu, lutetium-177; Akt, protein kinase B; mTOR, mammalian target of rapamycin; NET, neuroendocrine tumor; PI3K, phosphatidylinostitol-3-kinase; PRRT, peptide receptor radionuclide therapy; SSA, somatostatin analog; VEGFR, vascular endothelial growth factor receptor.

receptors 2 and 5 is common in NETs, and these receptors modulate hormone and growth-factor release, angiogenesis, and other functions.[19] SSAs are first-line therapy for well-differentiated G1 or G2 tumors with somatostatin receptor expression and are approved as treatment for the hormonal-induced syndromes, including carcinoid syndrome, associated with functional NETs. The PROMID and CLARINET studies demonstrated the antiproliferative effects of SSAs in patients with well-differentiated NETs.[20] Side effects of this class of drugs include GI disturbances and hyperglycemia, and patients may develop gallbladder issues with long-term treatment.[8,21] Significantly, treatment with SSAs results in tumor stabilization in 50% of patients.[22] However, the majority of patients treated with SSAs will go on to experience tumor progression.[23]

Octreotide is an octapeptide SSA available in a formulation for subcutaneous administration with an action that lasts for 8–12 h. It is also available in a long-acting release form given intramuscularly once every 28 days.[21] Octreotide has high affinity for somatostatin receptors 2 and 5, which are highly expressed in NETs, and works primarily by inhibiting somatostatin-stimulated secretion of hormones and growth factors. In the PROMID study, in patients with advanced well-differentiated midgut NETs, median time to tumor progression was 14.3 months in the octreotide group and 6 months in the placebo group (hazard ratio, 0.34).[24] Octreotide is indicated for treatment of carcinoid syndrome and functional pancreatic NETs and recommended to control growth of NETs.[15]

Lanreotide was developed to support the need for a longer-acting SSA. Lanreotide is a cyclic octapeptide SSA, administered by subcutaneous injection. Lanreotide sustained release has a half-life of 4.5 days and lanreotide autogel, an aqueous formulation supplied in prefilled syringes, is administered every 28 days.[18] Like octreotide, lanreotide has high affinity for somatostatin receptors 2 and 5. In the CLARINET study, patients with advanced G1 or G2, enteropancreatic, somatostatin receptor-positive NETs, treated with lanreotide, had a prolonged progression-free survival (PFS).[25] Lanreotide is approved to treat unresectable, well- to moderately differentiated, locally advanced or metastatic gastroenteropancreatic NETs, in addition to treatment of carcinoid syndrome.[20,15]

Tyrosine kinase inhibitor: sunitinib

Sunitinib is an oral receptor tyrosine kinase inhibitor indicated for the treatment of progressive, well-differentiated pNETs in patients with unresectable, locally advanced or metastatic disease. It predominantly targets VEGFRs but also blocks multiple other receptors.[8,26] Sunitinib is indicated for the treatment of pNETs only. Sunitinib improved PFS and objective response rate (ORR) as compared with placebo in patients with advanced, well-differentiated pancreatic NETs.[27] Common adverse events (AEs) associated with administration of sunitinib include diarrhea, neutropenia, and abdominal pain.[28] Activation of FGF receptor (FGFR)-1 and CSF-1R is a potential mechanism of tumor resistance to this and other VEGFR inhibitors.[16]

Mammalian target of rapamycin (mTOR) inhibitor: everolimus

Everolimus is an oral rapamycin analog which inhibits the PI3K/Akt and mTOR signaling pathway through direct interaction with mammalian target of rapamycin complex 1 (mTORC1).[29] Activation of the mTOR pathway has been shown to play a role in the proliferation of NETs.[29] In the RADIANT studies, patients treated with everolimus with carcinoid syndrome or functional NETs, advanced pNETs, and GI and lung NETs without carcinoid syndrome had prolonged PFS.[29] Recent evidence suggests that everolimus may also control symptoms in patients with functioning NETs.[30] Everolimus is currently approved for the treatment of NETs originating from the pancreas, GI tract, and lungs in patients with progressive disease. Everolimus is being tested in combination with other NET therapies including newer SSAs (pasireotide), monoclonal anti-VEGF antibodies (bevacizumab), cytotoxic agents (temozolomide), multi-kinase inhibitors (sorafenib), and PRRT.[29] Adverse events associated with administration of everolimus include stomatitis, rash, fatigue, infection, pulmonary toxicities, hyperglycemia, anemia, and thrombocytopenia.[29] Resistance to everolimus can develop due to the suppression of mTORC1, resulting in an increase in PI3K/Akt activity. Partial blockade of mTORC1 and lack of mammalian target of rapamycin complex 2 (mTORC2) blockade may also contribute to drug resistance. New treatments that inhibit both mTORC1 and mTORC2 are in development.[31]

Peptide receptor radionuclide therapy (PRRT): ^{177}Lu-DOTATATE

^{177}Lu-DOTATATE belongs to a class of NET therapies referred to as PRRT.[32] These therapies enable targeted delivery of radiation to the tumor through a radionuclide linked to a chelating molecule and a peptide receptor ligand. For NETs, the peptide ligand is an SSA. ^{177}Lu-DOTATATE binds to type 2 somatostatin receptors *via* octreotide, is internalized, and delivers beta radiation to the cell *via* lutetium-177. In the NETTER-1 study, treatment with ^{177}Lu-DOTATATE resulted in an increased PFS in patients with advanced midgut NETs.[33] 177Lu-DOTATATE is a treatment option for tumors that have progressed on SSA therapy. The major toxicity associated with this therapy is kidney proximal tubule injury.[34]

Cytotoxic chemotherapy

Cytotoxic chemotherapy can play a role in the treatment of bulky tumors, or tumors with extensive metastases at initial diagnosis, or NET disease that has progressed on first-line SSAs. Potential treatments include streptozotocin, a cytotoxic antitumor drug for symptomatic or advanced pNETs. Streptozotocin is used alone or in combination with other agents including 5 fluorouracil, an anti-metabolite, or doxorubicin, which is of limited use because of its risk of cardiotoxicity with a cumulative dose.[17] Another cytotoxic chemotherapeutic agent used to treat NETs is temozolomide. Temozolomide is typically administered alone or in combination with capecitabine, although these are not approved therapies for NETs. In a meta-analysis, the combination of temozolomide and capecitabine was found to be effective with acceptable toxicity for the treatment of advanced NETs.[35] Studies to support approved use of this combination chemotherapy or temozolomide alone are ongoing.[36,37]

Other NET therapies in development

Multiple new therapies are in clinical development for the treatment of NETs. There are several tyrosine kinase inhibitors with activity against VEGFR along with added receptor pharmacologies, including platelet-derived growth-factor receptor (PDGFR) and FGFR.[16] For example, lenvatinib is an oral, multi-receptor tyrosine kinase inhibitor that targets VEGFR1–3, FGFR1–4, PDGFRα, and stem cell factor receptor (KIT) and rearranged during transfection (RET).

Pazopanib is another oral tyrosine kinase inhibitor that targets VEGFR1–3, FGFR1–3, PDGFRα, PDGFRβ, and KIT. There are also therapies in clinical development that inhibit immune checkpoints by targeting PD-1 or PD-L1, based on studies that show high expression of PD-L1 in NETs.[12]

Combination therapies

Given the information on the molecular biology of NETs, available therapeutic options with different mechanisms of action are being combined in clinical studies to improve efficacy and overcome tumor resistance. However, the potential for increased toxicity of combination therapies also needs to be considered. In addition, the question of simultaneous administration *versus* the most efficacious sequencing of therapeutic administration remains to be addressed. To date, most combination therapy studies for the treatment of NETs have been exploratory and have not been tested in phase III registration studies.

One example of combination therapies being tested in the clinic is the monoclonal antibody directed against VEGF, bevacizumab, in combination with chemotherapeutic agents such as temozolomide or capecitabine.[26] While phase II studies showed clinical activity and an acceptable safety profile of this combination,[38] the results have not been demonstrated in a phase III study yet. Administration of everolimus and sunitinib is designed to act on both the mTOR pathway and VEGF signaling. However, only sequential treatment with everolimus and sunitinib has been studied in patients, and there was no significant difference in median PFS or overall survival, no matter which treatment was administered first.[39] The combination of PRRT with other types of therapeutic agents is another area of research aimed at improving patient response.[40] For example, the combination of PRRT and chemotherapy resulted in disease control in 38–55% of patients (depending on the imaging technique used), where either treatment alone had failed.[41] However, despite the increased interest and increasing number of studies combining PRRT with other therapies, there has yet to be any breakthrough in patient outcomes.[42] Finally, the combination of everolimus and lanreotide, compared with everolimus alone, is currently being tested in a phase III trial that started in April 2020 in Japan.[43]

Surufatinib

Background

A primary issue with current treatments for NETs is the development of tumor resistance. For example, resistance to tyrosine kinase inhibitors that block tumor angiogenesis may result from the induction of other pro-angiogenic pathways including FGFR and CSF-1R and include the participation of TAMs.[13] Two recently completed phase III studies of surufatinib, a new, oral, small-molecule inhibitor of VEGFR1–3, FGFR1, and CSF-1R, combines the inhibition of FGFR, which is known to be involved in resistance to VEGFR blockade, and the inhibition of CSF-1R to decrease tumor-immune evasion.[44,45]

Mechanism of action and preclinical data

Surufatinib (HMPL-012, previously known as sulfatinib) is an oral, small-molecule tyrosine kinase inhibitor that potently inhibits VEGFR1 (IC_{50} = 0.002 μmol/l), VEGFR2 (IC_{50} = 0.024 μmol/l), VEGFR3 (IC_{50} = 0.001 μmol/l), FGFR1 (IC_{50} 0.015 μmol/l), and CSF-1R (IC_{50} = 0.004 μmol/l).[46,47] In preclinical studies, the antiangiogenic and antitumor activity of surufatinib was demonstrated.[46,47] This unique combination of molecular activities inhibits tumor angiogenesis and regulates tumor-immune evasion (Figure 1; Table 2).

Phase I surufatinib clinical study

In a phase I study of surufatinib [ClinicalTrials.gov identifier: NCT02133157], the pharmacokinetics (PK), maximum tolerated dose (MTD), tumor response, safety, and recommended dose for phase II studies (RP2D) were evaluated in 77 patients with advanced solid tumors in a Chinese population.[46] PK evaluation showed no increase in drug exposure from a 300 mg to 350 mg once daily (QD) dose of surufatinib, warranting no further dose escalation. Thus, the MTD of surufatinib was not reached (NR) at doses up to 350 mg QD. Nine patients, including eight with NETs, had a confirmed partial response. A total of 15 patients, including 10 with NETs, achieved stable disease. This study included 21 patients with advanced NETs who were treated with surufatinib formulation 2. Surufatinib showed robust clinical activity in these patients, with an ORR of 38.1%, disease control rate (DCR) of 85.7%, and a median PFS of 16.9 months [95% confidence interval (CI), 9.5 to NR].[46]

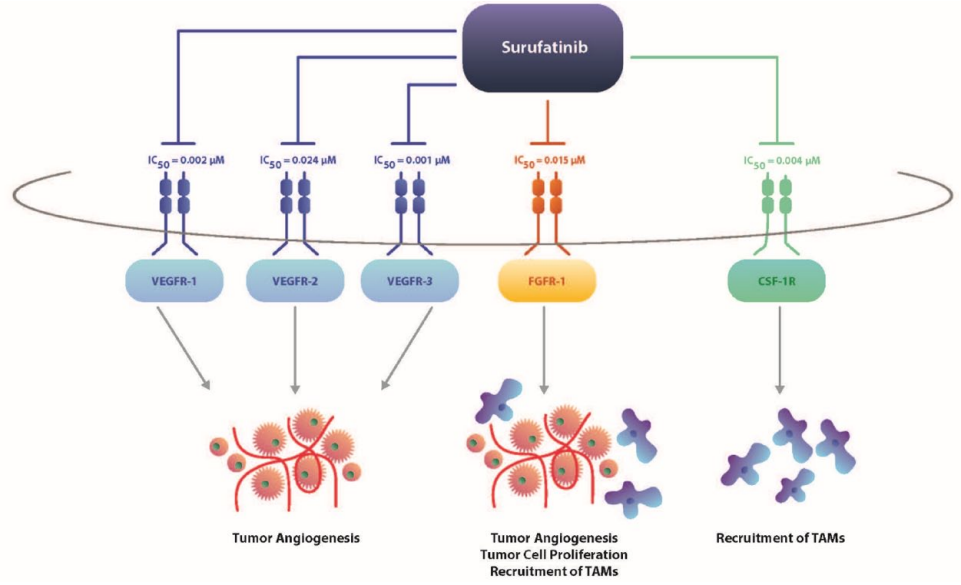

Figure 1. Surufatinib acts as a novel angio-immune kinase inhibitor by blocking activation of VEGFR1, VEGFR2, VEGFR3, FGFR-1, and CSF-1R.
CSF-1R, colony-stimulating factor-1 receptor; FGFR, fibroblast growth-factor receptor; IC_{50}, half maximal inhibitory concentration; TAM, tumor-associated macrophage; VEGFR, vascular endothelial growth-factor receptor.

Table 2. Summary of surufatinib characteristics.

Novel mechanism of action targeting VEGFR1, VEGFR2, VEGFR3, FGFR1, and CSF-1R
Demonstrated clinical efficacy in phase I and Ib/II studies in NET patients
Demonstrated clinical efficacy in two double-blind, placebo-controlled phase III studies in patients with well-differentiated G1/G2 pNETs and patients with G1/G2 epNETs
Clinical efficacy is not dependent on tumor origin
Demonstrated efficacy in populations in US and China
Tolerable safety profile

CSF, colony-stimulating factor; epNET, extrapancreatic neuroendocrine tumor; FGFR, fibroblast growth factor receptor; G1, grade 1; G2, grade 2; NET, neuroendocrine tumor; pNET, pancreatic neuroendocrine tumor; US, United States; VEGFR, vascular endothelial growth factor receptor.

Surufatinib was well tolerated up to 350 mg QD in this study. The most common AEs reported were similar to those seen with other VEGFR inhibitors and included proteinuria, hypertension, and diarrhea. The RP2D based on PK, safety and tolerability, and preliminary efficacy data in this phase I study was determined to be 300 mg QD.

Phase Ib/II surufatinib clinical study

In a multicenter, single-arm, open-label phase Ib/II study, patients with advanced, well-differentiated NETs, including both pNETs and extrapancreatic NETs (epNETs), were enrolled at seven Chinese clinical centers to further assess the safety and efficacy of surufatinib.[48] The primary endpoints in this study were investigator-assessed safety and ORR. Secondary endpoints included DCR, duration of response, PFS, safety, and PK. In the pNET cohort of 42 patients, the ORR was 19% (95% CI, 9–34%), and the DCR was 91% (95% CI, 77–97%). In the epNET cohort of 39 patients, the ORR was 15% (95% CI, 6–31%), and the DCR was 92% (95% CI, 79–98%). The median PFS

was 21.2 months (95% CI, 15.9–24.8) in pNET patients and 13.4 months (95% CI, 7.6–19.3) in epNET patients. The most common treatment-related AEs were proteinuria, diarrhea, and hypertension; again, similar to angiogenesis inhibitors. Dose modification and supportive care were used to manage AEs in this study.

Five circulating proteins including VEGF-A, FGF23, macrophage CSF (M-CSF), soluble VEGFR2 (sVEGFR-2), and basic FGF (bFGF) associated with the molecular actions of surufatinib were evaluated for changes and outcome association during this phase Ib/II study of surufatinib.[48] Increases in circulating VEGF-A, FGF23, and M-CSF, and decreases in sVEGFR-2 were demonstrated in the study.[48] Changes in these four proteins were consistent with previous studies with relevant kinase inhibitors.[49] These data suggest that circulating VEGF-A, FGF23, M-CSF, and sVEGFR-2 have the potential to be pharmacodynamic biomarkers for these drug targets. Interestingly, while bFGF levels increased in other tumor types with antiangiogenic drugs,[50,51] bFGF levels did not increase with surufatinib treatment in this study. The differential changes in bFGF, although they were measured in patients with different tumor types, suggest that increased FGF/FGFR signaling might not be the dominant mechanism for resistance to surufatinib.[48] Furthermore, higher sVEGFR-2 and lower bFGF levels at baseline associated with longer median PFS in the surufatinib study.[48]

Phase III surufatinib clinical studies

Surufatinib was tested in a Chinese population in two double-blind, placebo-controlled, phase III clinical studies conducted in parallel. The patient populations, for the two phase III surufatinib studies were separated into those with pNETs and those with epNETs. Inclusion criteria included an Eastern Cooperative Oncology Group performance status of 0 or 1 and progression on no more than two types of previous systemic regimens for advanced disease.[44,45] Surufatinib in Advanced Pancreatic NeuroEndocrine Tumors (SANET-p) tested the efficacy of surufatinib in pNETs. Surufatinib in Advanced Extrapancreatic Neuro Endocrine Tumors (SANET-ep) tested the efficacy of surufatinib in epNETs.

Surufatinib in advanced pancreatic neuroendocrine tumors (SANET-p). SANET-p was a multicenter, randomized, double-blind, placebo-controlled phase III study conducted in 21 hospitals in China [ClinicalTrials.gov identifier: NCT02589821].[44] Surufatinib was tested in 172 adults with progressive, advanced, well-differentiated pancreatic NETs, G1 or G2, with progression on two or fewer previous systemic regimes for advanced disease. The study included patients with aggressive pNETs with poor prognosis, and most patients had G2 tumors with liver metastasis and involvement of multiple organs. Patients with functional NETs that required treatment with long-acting SSAs, progression on other therapies that act on the VEGF system, clinically significant comorbidities, unstable brain metastases, or G3 tumors were excluded from the study. At the preplanned interim analysis, a total of 113 patients were randomized to the surufatinib group, and 59 patients were randomized to the placebo group.

In the SANET-p study, patients were given 300 mg surufatinib or placebo QD. The primary endpoint for the study was PFS as assessed by study investigators in the intention-to-treat population (including all randomized patients). Secondary outcomes included ORR, DCR, tumor shrinkage, time to response, duration of response, overall survival, and safety. This phase III study met its predefined early stopping success criteria at the preplanned interim analysis and was terminated based on recommendations from the independent data monitoring committee (IDMC). According to the investigator assessment at the interim analysis, the median PFS rate in patients treated with surufatinib was 10.9 months *versus* 3.7 months for placebo (hazard ratio, 0.49; 95% CI, 0.32–0.76; $p = 0.0011$), demonstrating that surufatinib was superior to placebo in the SANET-p study (Figure 2).[52] PFS also benefited surufatinib across major subgroups in the SANET-p study (Figure 3).[52]

The safety profile of surufatinib in the SANET-p study was consistent with previous surufatinib clinical studies.[46,48] The most common grade 3 or worse treatment-related AEs were hypertension, proteinuria, hypertriglyceridemia, and diarrhea.

The investigators attribute the statistically significant, clinically meaningful antitumor activity of surufatinib in the SANET-p study to its unique multipronged mechanism of action including inhibition of VEGF, FGF, and CSF-1 signaling.

While the efficacy in phase III trials is comparable between surufatinib and sunitinib in pNET

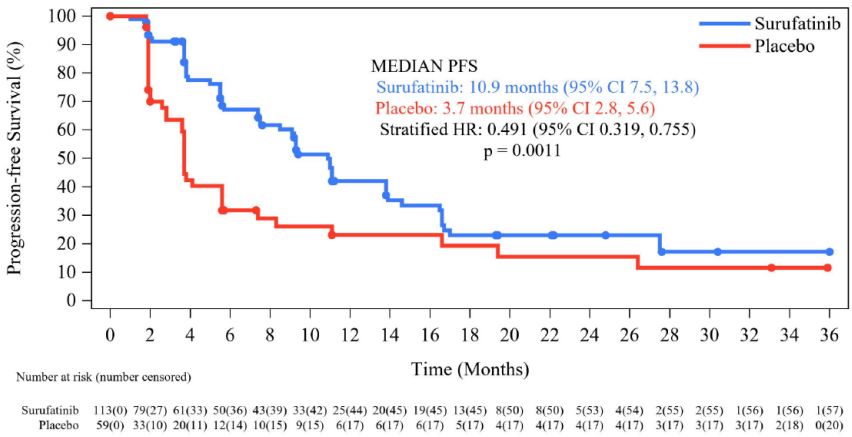

Figure 2. Progression-free survival in the SANET-p study (investigator-assessed).
CI, confidence interval; HR, hazard ratio; PFS, progression-free survival; SANET-p, surufatinib in advanced pancreatic neuroendocrine tumor.

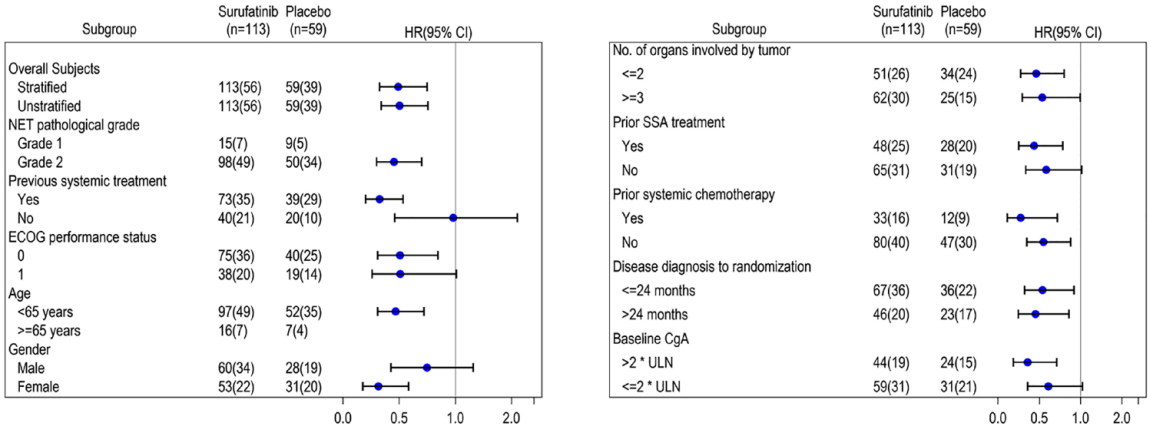

Figure 3. Progression-free survival benefit favored surufatinib across major subgroups in the SANET-p study (investigator-assessed).
CgA, chromogranin A; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; NET, neuroendocrine tumor; PFS, progression-free survival; SANET-p, surufatinib in advanced pancreatic neuroendocrine tumors; SSA, somatostatin analog; ULN, upper limit of normal.

patients, the kinase inhibition profile and the safety profile are somewhat different. Both inhibit VEGFR (1–3) and CSR-1; however, sunitinib does not possess significant inhibitory activity against FGFR-1.[53] Other than diarrhea, which is a treatment-emergent AE reported in both surufatinib and sunitinib trials, the most common grade 3 or greater treatment-related AEs associated with surufatinib were hypertension (38%), proteinuria (10%), and hypertriglyceridemia (7%).[44] For sunitinib, the most common grade 3 or greater treatment-related AEs were neutropenia (12%), hypertension (10%), and hand and foot syndrome (6%).[27] Median PFS in pNET patients treated with sunitinib was 11.4 months *versus* 5.5 months in the placebo group (hazard ratio, 0.42; 95% CI, 0.26 to 0.66; $p < 0.001$) and the ORR was 9.3% (95% CI, 3.2–15.4).[27] In comparison, median PFS in surufatinib-treated pNET patients was 10.9 months *versus* 3.7 months for placebo (hazard ratio, 0.49; 95% CI, 0.32–0.76; $p = 0.0011$) and the ORR was 19% (95% CI, 12–28%).[44] In addition to efficacy in pNETs, we describe the SANET-ep trial in the next section, where surufatinib also demonstrated superiority to placebo in patients with epNETs.[45]

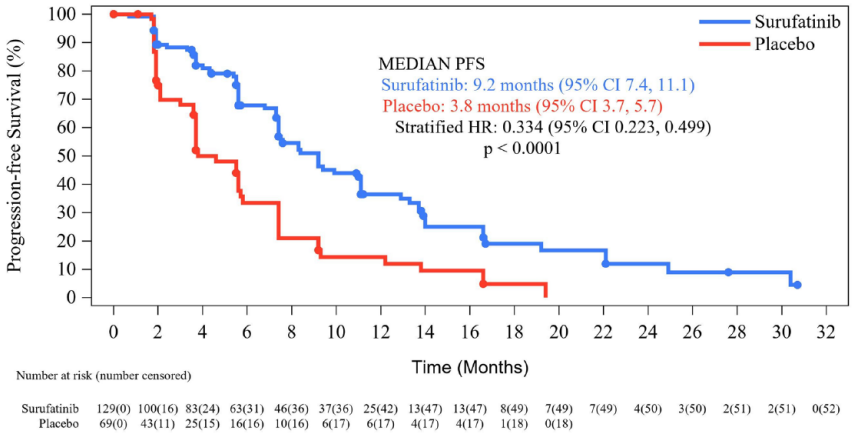

Figure 4. Progression-free survival in the SANET-ep study (investigator-assessed).
CI, confidence interval; HR, hazard ratio; PFS, progression-free survival; SANET-ep, surufatinib in advanced extrapancreatic neuroendocrine tumors.

Surufatinib in advanced extrapancreatic neuroendocrine tumors (SANET-ep). SANET-ep was a randomized, double-blind, placebo-controlled phase III study conducted in 24 hospitals in China [ClinicalTrials.gov identifier: NCT02588170] in parallel with the SANET-p study.[45] This was the first controlled phase III study demonstrating the efficacy of an antiangiogenic treatment in epNETs. Surufatinib was tested in 198 patients with unresectable or metastatic, well-differentiated G1 or G2 epNETs. Patients in the SANET-ep study had a range of primary tumor sites including GI tract (albeit low numbers of patients with midgut NETs and carcinoid syndrome), lung, thymus gland or mediastinum, liver, other, and unknown origin.[45] Patients with functioning NETs that required treatment with long-acting SSAs, progression on therapies that act on the VEGF system, or unstable brain metastases were excluded from the study. At the preplanned interim analysis, a total of 129 patients were randomized to the surufatinib group, and 69 patients were randomized to the placebo group.

In the SANET-ep study, patients were given 300 mg oral surufatinib or placebo QD. The primary endpoint for this study was investigator-assessed PFS. The secondary outcomes for the SANET-ep study were the same as those established for the SANET-p study. This study, like the SANET-p study, met its early stopping success criteria at the preplanned interim analysis and was terminated based on the recommendation of the IDMC. According to investigator assessment at the interim analysis, the median PFS in patients treated with surufatinib was 9.2 months *versus* 3.8 months for placebo (hazard ratio, 0.33; 95% CI, 0.22–0.50), demonstrating that surufatinib was superior to placebo in the SANET-ep study (Figure 4).[54] PFS also benefited surufatinib across major subgroups including tumor origin in the SANET-p study (Figure 5).[54]

US phase I study of surufatinib. In an ongoing study in US patients with pNETs and epNETs previously treated with everolimus and/or sunitinib, surufatinib has also demonstrated promising efficacy.[55] In addition, the PK and safety profile in US patients is similar to data collected in studies done in China.[44,45] As of January 2020, the ORR was 9.4% in a heavily pretreated patient population.[55]

Combination therapy with surufatinib

Given the efficacy and safety profile of surufatinib alone and its characterized molecular activities, several studies are planned to evaluate the co-administration of surufatinib with drugs that inhibit PD-1 to evaluate the safety and efficacy of this combination.

A phase I study [ClinicalTrials.gov identifier: NCT03879057] being conducted in China is evaluating the safety, tolerability, PK, and efficacy of surufatinib in combination with JS001 (toripalimab), a humanized anti-PD-1 monoclonal antibody, in patients with advanced solid tumors including NETs. Preliminary results indicate that the individual PK profiles of the drugs in

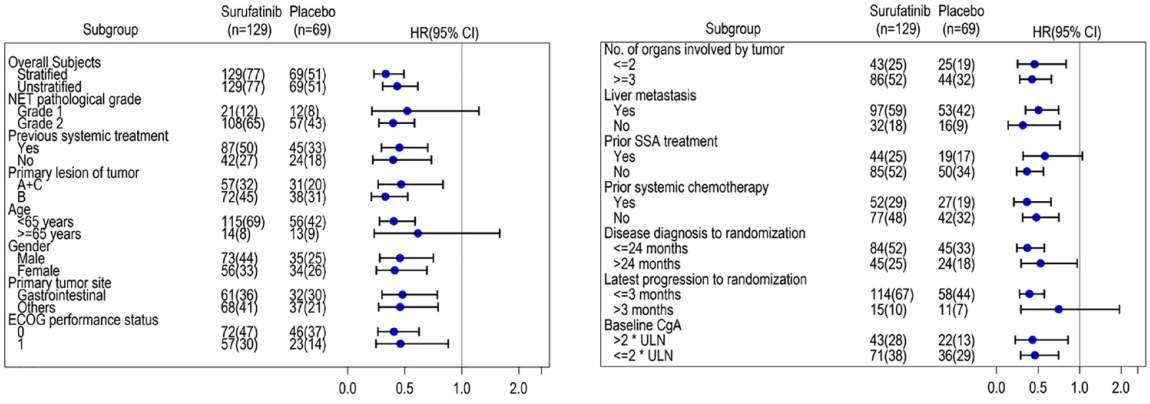

Figure 5. Progression-free survival benefit favored surufatinib across major subgroups in the SANET-ep study (investigator-assessed).

Tumor origin: A: jejunum, ileum, duodenum, thymus, cecum; B: lung, stomach, liver, appendix, colon, rectum; C: others or unknown origin.

CgA, chromogranin A; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; NET, neuroendocrine tumor; PFS, progression-free survival; SANET-ep, surufatinib in advanced extrapancreatic neuroendocrine tumors; SSA, somatostatin analog; ULN, upper limit of normal.

combination were comparable with those of surufatinib or toripalimab alone from previous clinical studies. The combination of drugs was well tolerated with no unexpected safety concerns. For the 21 NET patients, including those with G1 and G2 tumors (4 patients), G3 tumors (4 patients), and neuroendocrine carcinoma (13 patients), the ORR was 23.8% and the DCR was 81.0%.[56]

Another study is planned to evaluate the safety and efficacy of Innovent's TYVYT® (sintilimab injection), a fully humanized anti-PD-1 monoclonal antibody, in combination with surufatinib, in China, in patients with advanced solid tumors. TYVYT® is an immunoglobulin G4 monoclonal antibody, which binds to PD-1 molecules on the surface of T cells, blocks the PD-1/PD-L1 pathway, and reactivates T cells to kill cancer cells. The primary objective of the study is to evaluate the safety, tolerability, and initial antitumor efficacy of surufatinib in combination with TYVYT®. The first patient was dosed in July 2020.

An open-label phase Ib/II study of surufatinib in combination with BeiGene's tislelizumab is scheduled to begin in March 2021 in the US. Tislelizumab is a humanized IgG4 anti-PD-1 monoclonal antibody designed to minimize binding to the Fc gamma receptor (FcγR). Binding to the FcγR is believed to impair the antitumor properties of anti-PD-1 antibodies based on preclinical studies.[57] The study [ClinicalTrials.gov identifier: NCT04579757] will evaluate the safety, tolerability, PK, and efficacy in patients with advanced solid tumors and consist of dose finding (part 1) and dose expansion (part 2). Part 1 will be conducted to determine the RP2D and/or the MTD of surufatinib in combination with tislelizumab in patients with advanced or metastatic solid tumors who have progressed on, or tolerated, standard therapies. Part 2 will be an open-label, multicohort design to evaluate the antitumor activity of surufatinib in combination with tislelizumab in patients with specific types of advanced or metastatic solid tumors. Patients will receive the RP2D determined in part 1 of the study.

Conclusions

Current systemic therapies approved to treat NETs include SSAs, sunitinib (a tyrosine kinase inhibitor), mTOR inhibitors, PRRT, and cytotoxic chemotherapy. Both high tumor vascularization and immune evasion contribute to tumor progression. Combination therapies are being investigated in patients with NETs to improve efficacy and extend PFS as well as decrease tumor resistance, but few have progressed to phase III studies.

Surufatinib is a new, oral, small-molecule tyrosine kinase inhibitor that potently inhibits VEGFR1, VEGFR2, VEGFR3, FGFR1, and CSF-1R. Its unique mechanism of action, simultaneously inhibiting angiogenesis (VEGFR and FGFR1) and tumor-immune evasion (CSF-1R), has the potential to enhance antitumor activity.

The initial clinical profile of surufatinib in NETs was demonstrated in phase I and phase Ib/II studies. Biomarker data in the phase Ib/II study suggest that changes in circulating proteins (increases in VEGF-A, FGF23, and M-CSF, and decreases in VEGFR-2) have the potential to be pharmacodynamic biomarkers for these drug targets. Basic FGF levels did not increase with surufatinib treatment, suggesting that increased FGFR signaling might not be the dominant mechanism for resistance to surufatinib.

Two double-blind, placebo-controlled phase III studies were conducted in patients with well-differentiated G1/G2 pNETs (SANET-p) and epNETs (SANET-ep). Both studies demonstrated the statistically significant, clinically meaningful, antitumor activity of surufatinib compared with placebo, with a tolerable safety profile. While differences in the patient characteristics of the SANET trials compared with patients from the Western hemisphere are acknowledged, such as enrollment of a relatively low proportion of patients with NETs of small-bowel origin (8–9% in SANET-ep), subgroup analyses demonstrated superiority of surufatinib, suggesting overall results were not driven by a subset of patients. Therefore, the results of the SANET trials are generalizable to Western patients. This conclusion is further supported by an ongoing US study with surufatinib that has demonstrated promising efficacy and a similar PK and safety profile to studies done in China. Ongoing studies are evaluating the efficacy and safety of surufatinib in combination with other NET treatments. These positive results support the efficacy of surufatinib in patients with advanced, progressive, well-differentiated NETs, regardless of tumor origin. Surufatinib introduces a new treatment option with a novel mechanism of action for this growing patient population with unmet medical needs.

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Conflict of interest statement

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References

1. Hofland J, Kaltsas G and De Herder WW. Advances in the diagnosis and management of well-differentiated neuroendocrine neoplasms. *Endocr Rev* 2020; 41: 371–403.
2. Yao JC, Hassan M, Phan A, *et al*. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. *J Clin Oncol* 2008; 26: 3063–3072.
3. Dasari A, Shen C, Halperin D, *et al*. Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States. *JAMA Oncol* 2017; 3: 1335–1342.
4. Sackstein PE, O'Neil DS, Neugut AI, *et al*. Epidemiologic trends in neuroendocrine tumors: an examination of incidence rates and survival of specific patient subgroups over the past 20 years. *Semin Oncol* 2018; 45: 249–258.
5. Nagtegaal ID, Odze RD, Klimstra D, *et al*. The 2019 WHO classification of tumours of the digestive system. *Histopathology* 2020; 76: 182–188.
6. Cives M, Pelle E, Quaresmini D, *et al*. The tumor microenvironment in neuroendocrine tumors: biology and therapeutic implications. *Neuroendocrinology* 2019; 109: 83–99.
7. Oronsky B, Ma PC, Morgensztern D, *et al*. Nothing but NET: a review of neuroendocrine tumors and carcinomas. *Neoplasia* 2017; 19: 991–1002.
8. Cives M and Strosberg JR. Gastroenteropancreatic neuroendocrine tumors. *CA Cancer J Clin* 2018; 68: 471–487.
9. Jiao Y, Shi C, Edil BH, *et al*. DAXX/ATRX, MEN1, and mTOR pathway genes are frequently altered in pancreatic neuroendocrine tumors. *Science* 2011; 331: 1199–1203.
10. Pyonteck SM, Gadea BB, Wang HW, *et al*. Deficiency of the macrophage growth factor

CSF-1 disrupts pancreatic neuroendocrine tumor development. *Oncogene* 2012; 31: 1459–1467.

11. Keklikoglou I, Kadioglu E, Bissinger S, *et al.* Periostin limits tumor response to VEGFA inhibition. *Cell Rep* 2018; 22: 2530–2540.
12. Hasegawa S, Kobayashi N, Okubo N, *et al.* Pathological findings of the host immune reaction in the tumor microenvironment of gastroenteropancreatic neuroendocrine neoplasms. *Intern Med* 2020; 60: 977–983.
13. Cai L, Michelakos T, Deshpande V, *et al.* Role of tumor-associated macrophages in the clinical course of pancreatic neuroendocrine tumors (PanNETs). *Clin Cancer Res* 2019; 25: 2644–2655.
14. Albertelli M, Dotto A, Nista F, *et al.* Present and future of immunotherapy in neuroendocrine tumors. *Rev Endocr Metab Disord* 2021; 22: 615–636.
15. Pavel M, O'Toole D, Costa F, *et al.* ENETS consensus guidelines update for the management of distant metastatic disease of intestinal, pancreatic, bronchial neuroendocrine neoplasms (NEN) and NEN of unknown primary site. *Neuroendocrinology* 2016; 103: 172–185.
16. Cives M, Pelle E and Strosberg J. Emerging treatment options for gastroenteropancreatic neuroendocrine tumors. *J Clin Med* 2020; 9: 3655.
17. Krug S, Gress TM, Michl P, *et al.* The role of cytotoxic chemotherapy in advanced pancreatic neuroendocrine tumors. *Digestion* 2017; 96: 67–75.
18. Reubi JC and Schonbrunn A. Illuminating somatostatin analog action at neuroendocrine tumor receptors. *Trends Pharmacol Sci* 2013; 34: 676–688.
19. Krug S, Mordhorst JP, Moser F, *et al.* Interaction between somatostatin analogues and targeted therapies in neuroendocrine tumor cells. *PLoS One* 2019; 14: e0218953.
20. Gomes-Porras M, Cárdenas-Salas J and Álvarez-Escolá C. Somatostatin analogs in clinical practice: a review. *Int J Mol Sci* 2020; 21: 1682.
21. Costa F and Gumz B. Octreotide – a review of its use in treating neuroendocrine tumours. *Eur Endocrinol* 2014; 10: 70–74.
22. Stueven AK, Kayser A, Wetz C, *et al.* Somatostatin analogues in the treatment of neuroendocrine tumors: past, present and future. *Int J Mol Sci* 2019; 20: 3049.
23. Pozas J, San Román M, Alonso-Gordoa T, *et al.* Targeting angiogenesis in pancreatic neuroendocrine tumors: resistance mechanisms. *Int J Mol Sci* 2019; 20: 4949.
24. Rinke A, Müller HH, Schade-Brittinger C, *et al.* Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide lar in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID study group. *J Clin Oncol* 2009; 27: 4656–4663.
25. Caplin ME, Pavel M, Ćwikła JB, *et al.* Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *N Engl J Med* 2014; 371: 224–233.
26. Beyens M, Vandamme T, Peeters M, *et al.* Resistance to targeted treatment of gastroenteropancreatic neuroendocrine tumors. *Endocr Relat Cancer* 2019; 26: R109–R130.
27. Raymond E, Dahan L, Raoul JL, *et al.* Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. *N Engl J Med* 2011; 364: 501–513.
28. Valle JW, Borbath I, Rosbrook B, *et al.* Sunitinib in patients with pancreatic neuroendocrine tumors: update of safety data. *Future Oncol* 2019; 15: 1219–1230.
29. Lee L, Ito T and Jensen RT. Everolimus in the treatment of neuroendocrine tumors: efficacy, side-effects, resistance, and factors affecting its place in the treatment sequence. *Expert Opin Pharmacother* 2018; 19: 909–928.
30. Ito T, Lee L and Jensen RT. Treatment of symptomatic neuroendocrine tumor syndromes: recent advances and controversies. *Expert Opin Pharmacother* 2016; 17: 2191–2205.
31. Chamberlain CE, German MS, Yang K, *et al.* A patient-derived xenograft model of pancreatic neuroendocrine tumors identifies sapanisertib as a possible new treatment for everolimus-resistant tumors. *Mol Cancer Ther* 2018; 17: 2702–2709.
32. Das S, Al-Toubah T, El-Haddad G, *et al.* ^{177}Lu-dotatate for the treatment of gastroenteropancreatic neuroendocrine tumors. *Expert Rev Gastroenterol Hepatol* 2019; 13: 1023–1031.
33. Strosberg J, El-Haddad G, Wolin E, *et al.* Phase 3 trial of ^{177}Lu-dotatate for midgut neuroendocrine tumors. *N Engl J Med* 2017; 376: 125–135.
34. Stolniceanu CR, Nistor I, Bilha SC, *et al.* Nephrotoxicity/renal failure after therapy with ^{90}Yttrium- and ^{177}Lutetium-radiolabeled somatostatin analogs in different types of

neuroendocrine tumors: a systematic review. *Nucl Med Commun* 2020; 41: 601–617.

35. Lu Y, Zhao Z, Wang J, *et al*. Safety and efficacy of combining capecitabine and temozolomide (CAPTEM) to treat advanced neuroendocrine neoplasms: a meta-analysis. *Medicine (Baltimore)* 2018; 97: e12784.
36. de Mestier L, Walter T, Evrard C, *et al*. Temozolomide alone or combined with capecitabine for the treatment of advanced pancreatic neuroendocrine tumor. *Neuroendocrinology* 2020; 110: 83–91.
37. Bongiovanni A, Liverani C, Foca F, *et al*. Temozolomide alone or combined with capecitabine for the treatment of metastatic neuroendocrine neoplasia: a "real world" data analysis. *Neuroendocrinology*. Epub ahead of print 20 November 2020. DOI: 10.1159/0005 13218.
38. Mitry E, Walter T, Baudin E, *et al*. Bevacizumab plus capecitabine in patients with progressive advanced well-differentiated neuroendocrine tumors of the gastro-intestinal (GI-NETS) tract (BETTER trial)–a phase II non-randomised trial. *Eur J Cancer* 2014; 50: 3107–3115.
39. Angelousi A, Kamp K, Kaltsatou M, *et al*. Sequential everolimus and sunitinib treatment in pancreatic metastatic well-differentiated neuroendocrine tumours resistant to prior treatments. *Neuroendocrinology* 2017; 105: 394–402.
40. Adant S, Shah GM and Beauregard JM. Combination treatments to enhance peptide receptor radionuclide therapy of neuroendocrine tumours. *Eur J Nucl Med Mol Imaging* 2020; 47: 907–921.
41. Yordanova A, Ahrens H, Feldmann G, *et al*. Peptide receptor radionuclide therapy combined with chemotherapy in patients with neuroendocrine tumors. *Clin Nucl Med* 2019; 44: e329–e335.
42. Chan TG, O'Neill E, Habjan C, *et al*. Combination strategies to improve targeted radionuclide therapy. *J Nucl Med* 2020; 61: 1544–1552.
43. Shimoyama R, Hijioka S, Mizuno N, *et al*. Study protocol for a multi-institutional randomized phase III study comparing combined everolimus plus lanreotide therapy and everolimus monotherapy in patients with unresectable or recurrent gastroenteropancreatic neuroendocrine tumors; Japan Clinical Oncology Group study JCOG1901 (STARTER-NET study). *Pancreatology* 2020; 20: 1183–1188.
44. Xu J, Shen L, Bai C, *et al*. Surufatinib in advanced pancreatic neuroendocrine tumours (SANET-p): a randomised, double-blind, placebo-controlled, phase 3 study. *Lancet Oncol* 2020; 21: 1489–1499.
45. Xu J, Shen L, Zhou Z, *et al*. Surufatinib in advanced extrapancreatic neuroendocrine tumours (SANET-ep): a randomised, double-blind, placebo-controlled, phase 3 study. *Lancet Oncol* 2020; 21: 1500–1512.
46. Xu JM, Wang Y, Chen YL, *et al*. Sulfatinib, a novel kinase inhibitor, in patients with advanced solid tumors: results from a phase I study. *Oncotarget* 2017; 8: 42076–42086.
47. Zhou J, Ni J, Cheng M, *et al*. *Preclinical evaluation of sulfatinib, a novel angio-immuno kinase inhibitor targeting VEGFR, FGFR1 and CSF1R kinases*. *Proceedings of the American Association for Cancer Research Annual Meeting*, 1–5 April 2017, Washington, DC, Philadelphia. Abstract 4187.
48. Xu J, Li J, Bai C, *et al*. Surufatinib in advanced well-differentiated neuroendocrine tumors: a multicenter, single-arm, open-label, phase Ib/II trial. *Clin Cancer Res* 2019; 25: 3486–3494.
49. Zurita AJ, Khajavi M, Wu HK, *et al*. Circulating cytokines and monocyte subpopulations as biomarkers of outcome and biological activity in sunitinib-treated patients with advanced neuroendocrine tumours. *Br J Cancer* 2015; 112: 1199–1205.
50. Batchelor TT, Sorensen AG, Di Tomaso E, *et al*. AZD2171, a pan-VEGF receptor tyrosine kinase inhibitor, normalizes tumor vasculature and alleviates edema in glioblastoma patients. *Cancer Cell* 2007; 11: 83–95.
51. Kopetz S, Hoff PM, Morris JS, *et al*. Phase II trial of infusional fluorouracil, irinotecan, and bevacizumab for metastatic colorectal cancer: efficacy and circulating angiogenic biomarkers associated with therapeutic resistance. *J Clin Oncol* 2010; 28: 453–459.
52. Xu J, Shen L, Bai C, *et al*. 1156o - surufatinib (s) for patients (pts) with advanced pancreatic neuroendocrine tumours (SANET-p): a randomized, double-blind, placebo (p)-controlled phase III trial (NCT02589821). *Ann Oncol* 2020; 31(Suppl. 4): S711–S724.
53. Zhao Y and Adjei AA. Targeting angiogenesis in cancer therapy: moving beyond vascular endothelial growth factor. *Oncologist* 2015; 20: 660–673.
54. Xu J, Shen L, Zhou Z, *et al*. 4979 - Efficacy and safety of surufatinib in patients with well-differentiated advanced extrapancreatic

neuroendocrine tumors (nets): results from the randomized phase III study (SANET-ep). *Ann Oncol* 2019; 30(Suppl. 5): V851–V934.

55. Dasari A, Li D, Sung M, *et al*. Efficacy and safety of surufatinib in United States (US) patients (pts) with neuroendocrine tumors (NETs). *J Clin Oncol* 2020; 38: 4610–4610.

56. Lu M, Cao Y, Gong J, *et al*. AACR2020: a phase I trial of surufatinib plus toripalimab in patients with advanced solid tumor. *Cancer Res* 2020; 80(Suppl. 16): CT142.

57. Liu SY and Wu YL. Tislelizumab: an investigational anti-PD-1 antibody for the treatment of advanced non-small cell lung cancer (NSCLC). *Expert Opin Investig Drugs* 2020; 29: 1355–1364.