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Systematic Review

Tyrosine kinase inhibitors in patients with neuroendocrine neoplasms: a systematic literature review

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Abstract

Background: Several tyrosine kinase receptors inhibitors (TKIs) have demonstrated antiproliferative effects in well-differentiated neuroendocrine tumors (NETs). We aimed to summarize and appraise the current evidence of the efficacy of TKIs in patients with different types of NETs.

Methods: We performed a systematic review of clinical trials of TKIs in patients with advanced gastroenteropancreatic or lung NETs (PROSPERO registration number: CRD42024507379). Population characteristics, efficacy, and safety results were summarized by type of NET.

Results: Twenty-eight studies were eligible, totaling 2284 patients. While sunitinib remains the only Food and Drug Administration-approved TKI in patients with NETs (for patients with pancreatic well-differentiated NETs), recent placebo-controlled randomized trials have demonstrated improved response rates and progression-free survival for patients with progressive and pre-treated well-differentiated pancreatic (cabozantinib or surufatinib) or gastrointestinal (GI) NETs (pazopanib, cabozantinib, or surufatinib). There is limited evidence to support the use of a TKI in patients with lung or grade 3 NETs. The toxicity associated with TKIs follows a class effect, with a significant proportion of patients experiencing fatigue, hypertension, and hand–foot skin reactions.

Conclusion: TKIs are effective therapies in patients with pancreatic or GI well-differentiated NETs and should be part of the therapeutical sequencing of these patients.

Keywords: clinical trial, neuroendocrine tumors, tyrosine kinase inhibitor

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Introduction

Neuroendocrine neoplasms represent a heterogeneous group of cancers with variable prognoses and responses to therapies. Their incidence and scientific awareness have increased, resulting in frequently updated classifications.[1,2] The extent of treatment strategies includes surgery, liver-directed therapies, somatostatin analogs, peptide receptor radionuclide therapy, chemotherapy, and molecular-targeted agents. Overall, more aggressive tumors are treated with chemotherapy (mostly alkylating-based or oxaliplatin-based regimens) and those patients with indolent disease can be managed by somatostatin analogs or targeted therapies.

Neuroendocrine tumor (NET) cells overexpress various types of proangiogenic molecules and receptors, and their dysregulation plays a role in the growth of the well-differentiated NET, which are generally hypervascular tumors.[3,4] Hypervascularization in NET, differently from other solid tumors, has not been linked to aggressiveness as high vascular density is a hallmark of low-grade NET.[5] Yet, tumor hypervascularity can be considered a target for therapies. Several growth factors, such as vascular endothelial growth factors (VEGF), platelet-derived growth factor (PDGF) and their receptors, and tyrosine kinase pathways, are involved in angiogenesis,

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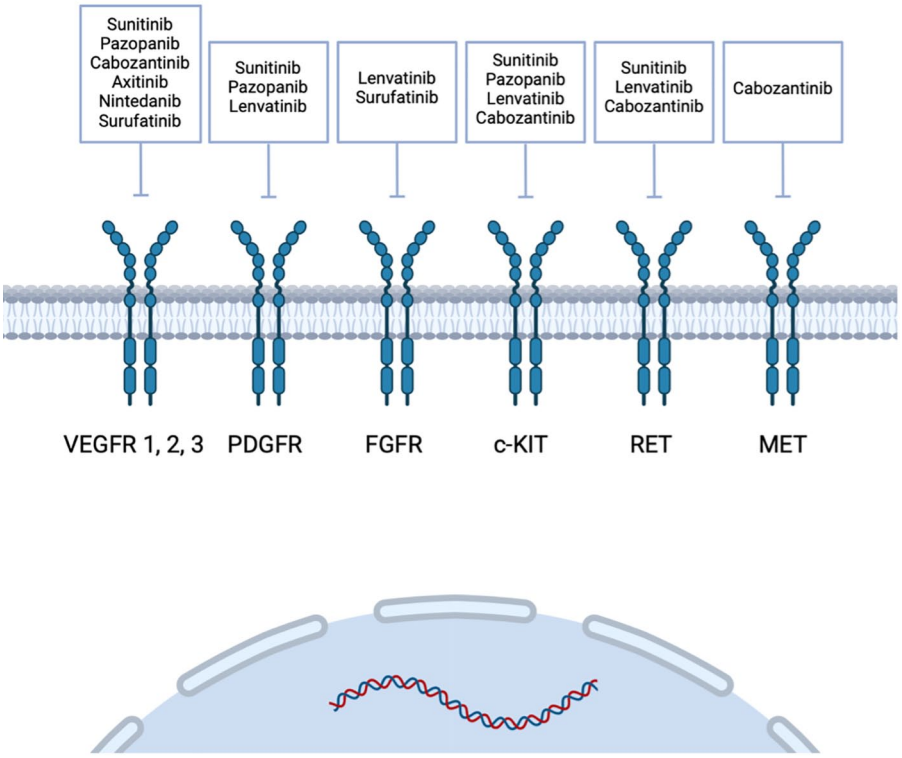

Figure 1. Tyrosine kinase inhibitors studied in neuroendocrine neoplasms and their respective targets.
Source: Created with BioRender.com.
c-KIT, stem-cell factor receptor (CD117); FGFR, fibroblast growth factor receptors; MET, hepatocyte growth factor receptor; PDGFR, platelet-derived growth factor receptors; RET, rearranged during transfection; VEGFR, vascular endothelial growth factor receptor.

tumor growth, and progression in NET.[3,5,6] Thus, inhibition of tyrosine kinase receptors, particularly those with antiangiogenic properties, could result in antiproliferative effects in NET (Figure 1).

Sunitinib, an oral multi-target tyrosine kinase inhibitor (TKI), in 2011, confirmed the hypothesis that antiangiogenic agents were effective against certain types of NET. Sunitinib inhibits platelet-derived growth factor receptor (PDGFR)α/β, vascular endothelial growth factor receptor (VEGFR) 1–3, fetal liver kinase-3, colony-stimulating factor 1 (CSF1) receptor, and rearranged during transfection (RET) signaling, and was evaluated in phase III, double-blind, placebo-controlled trial at 37.5 mg per day in 171 patients with pre-treated advanced G1–2 pancreatic NET (PanNET).[7–9] The trial terminated early because of positive results in the interim analysis of progression-free survival (PFS). Sunitinib showed a prolonged PFS (median, 11.4 vs 5.5 months; hazard ratio (HR), 0.42; $p < 0.001$) and a higher response rate (RR) (9.3% vs 0%; $p = 0.007$). A post hoc analysis adjusted for crossover suggested sunitinib increased overall survival (OS).[10] A phase IV trial confirmed the efficacy and safety of sunitinib in patients with metastatic well-differentiated PanNET.[11]

After more than a decade, sunitinib remains the only TKI approved by the Food and Drug Administration (FDA) for the treatment of patients with advanced NET. Despite not leading to drug registrations, subsequent studies have tested other TKIs in patients with different types of NET (Figure 1), with heterogeneous results.[7,12]

This systematic review aimed to summarize and critically appraise the scientific evidence for TKIs in patients with advanced NET.

Methods

Search and eligibility

We performed a systematic review of the efficacy of TKIs in patients with advanced NET as

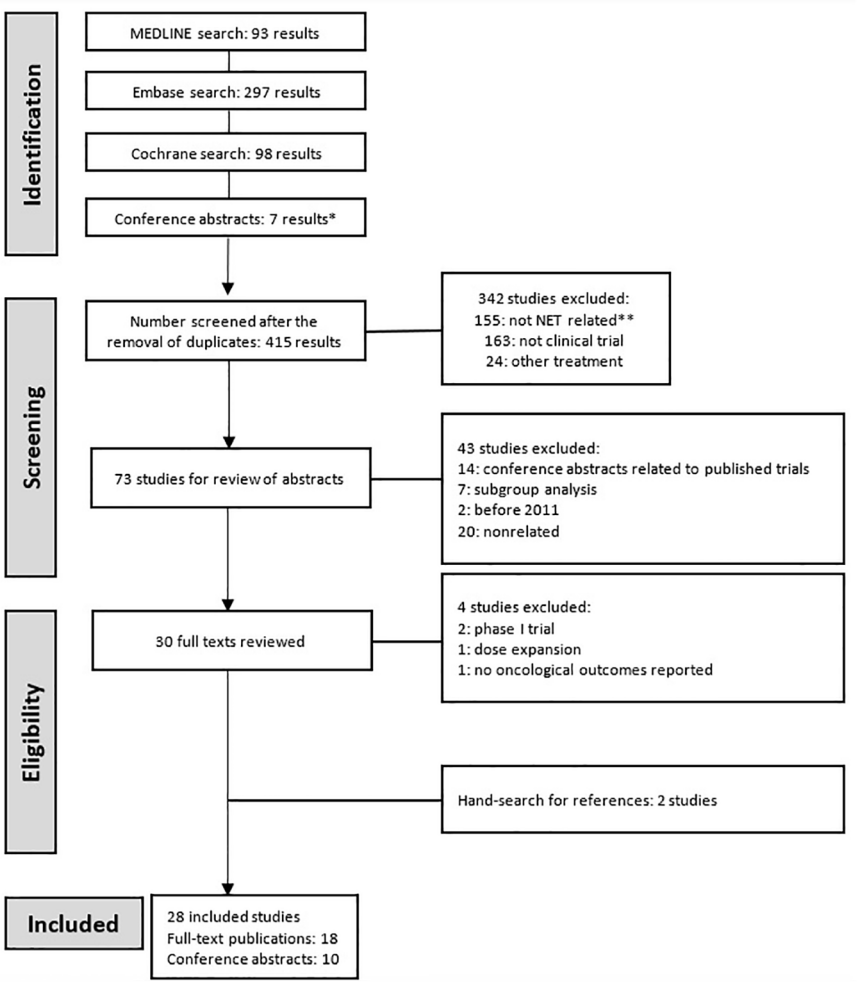

Figure 2. PRISMA flowchart for search strategy and study selection.
*Identified only as a conference abstract.
**Not included in this review: pheochromocytoma, paraganglioma, Merkel cell carcinoma, small-cell lung cancer, and thyroid origin.
PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis.

reported by clinical trials. This systematic review was performed in accordance with the Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis[13] guideline and was registered in the PROSPERO database (CRD42024507379).

Eligible studies were clinical trials or prospective cohorts that tested a TKI in monotherapy or combination with another therapy in patients with advanced or metastatic NET of gastroenteropancreatic (GEP), lung, or unknown origins. We excluded dose-finding or first-in-human clinical trials and trials in other types of endocrine or NETs (pheochromocytoma, paraganglioma, Merkel cell carcinoma, small-cell lung cancer, or thyroid cancer).

We sought eligible studies in PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), and EMBASE databases from January 2011 (since the publication of the landmark sunitinib phase III trial) until December 2023.[7] A supplementary search of congress abstracts published between 2011 and 2023 was carried out for the annual meetings of the American Society of Medical Oncology (ASCO), ASCO Gastrointestinal Symposium, the North American Neuroendocrine Tumor Society, the European Society for Medical Oncology, and the European Society of Neuroendocrine Tumors. No language restrictions were imposed.

Duplicate publications were sorted out and if an abstract resulted in a full publication, the latter

was selected. In addition, the references from the included articles were searched manually for any additional studies (Figure 2).

Two authors (R.G.T. and F.P.C.) independently searched for eligible studies and extracted predefined data in a standardized data collection sheet. For all data, disagreements were resolved by consensus among the authors.

Data extraction

For each study, the following data were collected: year of publication, type of publication (abstract or article), study design (randomized clinical trial, prospective cohort), number of patients, primary NET site, grade (and respective WHO classification), Ki-67 index, type of intervention(s), including regimens, and dosages, median follow-up times, and oncological outcomes (RR, PFS, OS, and rates and types of grade 3 or higher adverse events).

Results

The search yielded 415 entries after duplicate reports were removed. Of the remaining, 28 studies met the predefined inclusion criteria, totaling 2284 patients. Figure 1 describes the selection of eligible studies.

Pancreatic origin

The summary of studies is depicted in Table 1. Uncontrolled clinical trials have suggested that pazopanib or lenvatinib can be effective for patients with progressive well-differentiated advanced PanNET.

Pazopanib, a multitargeted agent against VEGFR 1–3, PDGFRα/β, and proto-oncogene c-Kit, was tested in single-arm phase II trials in patients with advanced PanNET.[14–17] In the trial by Phan et al.,[15] pazopanib 800 mg/day, in association with octreotide, showed antitumor activity in the PanNET cohort with 32 patients. The combined treatment demonstrated an RR of 21.9%, a median PFS of 14.4 months, and a median OS of 25 months.[15] The PAZONET trial evaluated pazopanib 800 mg/day in monotherapy; among the 18 patients with advanced PanNET, an objective RR was observed in 9% and the median PFS was 12.8 months.[16] The most frequent grade 3 or higher toxicities were hypertension (12%), fatigue (8%), and diarrhea (6%).

Lenvatinib, an inhibitor of VEGFR 1–3, fibroblast growth factor receptor 1–4 (FGFR 1–4), PDGFRα/β, and c-KIT, was tested in the parallel non-comparative phase II TALENT trial.[18,19] In the cohort of 55 patients with advanced PanNET (of which 48% had tumors with a Ki-67 higher than 10%, and highly pre-treated), lenvatinib 24 mg/day led to a partial response in 42% of cases and the median PFS was 15.6 months. Patients were highly pretreated, with 86% of patients having received prior SSA, 69% had prior everolimus, 33%, had chemotherapy, and 29% were previously exposed to sunitinib. The most frequent grade 3 or 4 adverse events were hypertension (22%), vomiting (9%), and diarrhea (7%).

Two other TKIs, surufatinib and cabozantinib, were investigated in patients with advanced PanNET in placebo-controlled randomized clinical trials.

Surufatinib, former sulfatinib, is a novel small molecule that simultaneously inhibits tumor angiogenesis (via VEGFR 1–3, and FGFR) and immune evasion (via macrophage CSF1 receptor).[20,21] Surufatinib was evaluated in phase III placebo-controlled trial in 172 Chinese patients with advanced G1/G2 PanNET.[22] Almost 90% of patients had G2 tumors, with 65% having received previous systemic treatments. The RR was 19% versus 2% ($p = 0.0021$), and the median PFS was 10.9 versus 3.7 months (HR 0.34, $p < 0.0001$), favoring surufatinib against placebo. Common grade 3 or higher adverse events included hypertension (38%), proteinuria (10%), hypertriglyceridemia (7%), and diarrhea (4%).

Cabozantinib is a multi-kinase inhibitor with strong antagonist activity against hepatocyte growth factor receptor (MET) and VEGFR2, also targeting KIT, RET, AXL, TIE2, and FLT3.[23] Cabozantinib 60 mg daily was evaluated in a recent phase III, double-blinded, placebo-controlled clinical, in patients with advanced G1–3 PanNET or extra-pancreatic NET who have progressive disease at least one prior line of therapy, not including somatostatin analogs.[24] The trial randomized each NET group to either cabozantinib or placebo. In the PanNET cohort, 63% had grade 2 NET and 10% had G3 NET, and patients had a median of 3 lines of prior therapies, including everolimus, temozolomide and capecitabine, and radioligand therapy. The study was closed early after the efficacy results of the second

interim analyses favored cabozantinib, with a median PFS of 11.4 versus 3 months. The overall RR was 18% versus 6%, favoring cabozantinib. At a median follow-up time of 16.7 months, there was no difference in OS (median of 43.5 vs 31 months). Grade 3 or higher occurred in 63% of patients, with the most common ones being hypertension (27%), fatigue (13%), thromboembolic event (12%), hand–foot syndrome (10%), and hyperglycemia (8%).

Gastrointestinal origin

Overall, TKIs demonstrated less efficacy in patients with advanced gastrointestinal (GI) NET when compared with those with PanNET. Table 2 describes the results of the eligible studies.

Pazopanib 800 mg daily was investigated in a phase III placebo-controlled trial with 171 patients with advanced GI NET.[25] The trial, published in abstract format, demonstrated an improvement in median PFS of 11.6 versus 8.5 months (HR 0.53, $p = 0.0005$), with no impact on OS, 41.3 versus 42.3 months (HR 1.13, $p = 0.7$). RR was not presented. In the trial by Phan et al.,[15] pazopanib in association with octreotide was evaluated in a GI NET cohort of 20 patients. The combination led to a median PFS of 12.2 months and a median OS of 18.5 months but reported no objective responses.

A single-arm phase II trial of cabozantinib in patients with GI NET reported an RR of 15% and a median PFS of 31.4 months.[26]

In the G1/G2 GI-NET cohort of the TALENT trial with lenvatinib, 16.4% of patients had an objective response and their median PFS was 15.7 months.[19]

Lung origin

Metastatic lung NETs (excluding small cell lung cancer) are rare and very few studies have reported on the efficacy of TKIs in this NET.

A single-arm phase II trial evaluated pazopanib in 44 patients (5 lung and 3 thymic NET patients) with previously treated advanced NETs. Patients had received at least one systemic treatment, with nearly half pretreated with a TKI and/or everolimus). The median PFS was only 3.4 months for patients with lung/thymic NETs and this was significantly inferior when

Table 1. Summary of studies of pancreatic neuroendocrine tumors.

TKI	Study	Trial phase line	*N*, population	Previous progression	NEN grade	Ki-67 > 10% (%)	Previous systemic therapies	Design treatment arms	Response rate (%)	PFS (months)	OS (months)	Main drug-related grades 3–4 toxicities (%)
Sunitinib	Raymond et al. (2011)[8,11]	III ≥1	171, pNET	Within the previous 12 months	G1 and G2 (<10%)	8	None (31%) SSA (36%) ChT (69%)	RCT Sunitinib 37.5 mg daily + BSC Placebo + BSC	9.3 0	12.6[a] 5.8	38.6[b] 29.1	Neutropenia (12), hypertension (10), palmar-plantar erythrodysesthesia (6)
Sunitinib	Raymond et al. (2018)[12,40]	IV ≥1	106, pNET	Within the previous 12 months	G1 (23%) G2 (74%) G3 (3%)	—	None (57%) SSA (48%) ChT (42%)	Sunitinib 37.5 mg daily	24.5	11.1	37.8	Neutropenia (21), thrombocytopenia (8), hand–foot syndrome (7), hypertension (6), diarrhea (6)
Sunitinib	Ito et al. (2019)	II ≥1	12, pNET	Within the previous 12 months	Well-differentiated[c]	—	None (33%) SSA (50%) ChT (50%)	Sunitinib 37.5 mg daily	50	16.8	NR	Neutropenia (33), diarrhea (8), thrombocytopenia (8)
Sunitinib	Grande et al. (2021)	II ≥1	17, pNET	—	G1 (12%), G2 (88%)	47	None (59%) SSA (41%)	Sunitinib 37.5 mg daily + Evofosfamide i.v.	17.6	10.4	NR	Neutropenia (35), fatigue (18), hypertension (12), thrombocytopenia (12)
Sunitinib	Baudin et al. (2022)	II 2	84, pNET	Within the previous 12 months	G1, G2, and G3	37	ChT (57%)	^{177}Lu-DOTATATE Sunitinib 37.5 mg daily	—	20.7[d] 11.0	—	PRRT: hematological (12), hypertension (12), fatigue (7) Sunitinib: hematological (24), hypertension (19), fatigue (12)
Pazopanib	Phan et al. (2015)[16]	II >1	32, pNEN; 20, Carcinoid tumors[e] (11 small bowel)	Progressive disease (85% pNET and 66% carcinoid tumors)	G1 (75%) G2 (25%)	—	SSA (100%), Everolimus (25%[f] and 30%[g]), ChT (66%[f] and 25%[g])	Pazopanib 800 mg daily and depot octreotide	21.9 (pNEN) 0 (carcinoid tumors)	14.4 (pNEN) 12.2 (carcinoid tumors)	25 (pNEN) 18.5 (carcinoid tumors)	Hypertension (12), fatigue (8), diarrhea (6), neutropenia (6)

(Continued)

Table 1. (Continued)

TKI	Study	Trial phase line	*N*, population	Previous progression	NEN grade	Ki-67 > 10% (%)	Previous systemic therapies	Design treatment arms	Response rate (%)	PFS (months)	OS (months)	Main drug-related grades 3–4 toxicities (%)
Pazopanib	Grande et al. (2015)[17]	II ⩾ 1	44 NET; 33 GEP (18 pancreases), 5 lungs and 3 thymic NET	Within the previous 12 months	G1 and G2	11	ChT (38%), TKI (36%), Everolimus (25%), SSA (80%)	Pazopanib 800 mg daily	9	9.5 (all population) 12.8 (pNET) 10 (GI NET) 3.4 (lung and thymic NETs)	—	Asthenia (16%), hepatotoxicity (16%), diarrhea (9%), hypertension (9%)
Cabozantinib	Chan et al. (2017)[28]	II >1	41, GI 20, pNET	Yes	G1 and G2	—	—	Cabozantinb 60 mg daily	15 GI 15 pNET	31.4 GI 21.8 pNET	—	Hypertension (13), hypophosphatemia (11), diarrhea (10), lymphopenia (7), fatigue (5)
Cabozantinib	Chan et al. (2023)[25]	III ⩾	197, epNET (109 GI NET and 39 lung NET) 93, pNET	Within the previous 12 months	EpNET: G1 (24%) G2 (64%) G3 (7%) pNET: G1 (20%) G2 (63%) G3 (10%)	—	EpNET: everolimus (67%), Lu177 (58%), ChT (41%); pNET: everolimus (80%), Lu177 (56%), sunitinib (27%), ChT (61%)	RCT: Cabozantinib 60 mg daily Placebo	epNET (4 vs 1) pNET (18 vs 6)	epNET (8.3 vs 3.2)[a] pNET (11.4 vs 3)[a]	epNET (21.9 vs 22.4) pNET (43.5 vs 31)	Hypertension (27), fatigue (14), thromboembolic event (12), diarrhea (10), hand–foot syndrome (10)
Lenvatinib	Capdevila et al. (2021)[20]	II >1	55 pNET 56 GI NET	Within the previous 12 months	pNET: G1 (22%) G2 (76%) GI NET: G1 (38%) G2 (61%)	48 pNET 24 GI NET	SSA (86% pNET; 100% GI NET), everolimus (69% pNET), Sunitinib (29% pNET), ChT (32% pNET)	Lenvatinib 24 mg daily	44 pNET 16 GI NET	15.6 pNET 15.7 GI NET	32 pNET NR GI NET	Hypertension (22), fatigue (11), diarrhea (11), vomiting (8)
Surufatinib	Xu et al. (2019)[33]	Ib/II >1	42 pNET 39 epNET (14 rectum, 4 lung NET)	—	G1(20%) G2 (80%)	—	SSA (52%) ChT (28%) TKI (22%) Everolimus (15%)	Surufatinib 300 mg daily	19 pNET 15 epNET	21.2 pNET 13.4 epNET	—	Hypertension (33), proteinuria (12), hyperuricemia (10), diarrhea (6), hypertriglyceridemia (6)
Surufatinib	Xu et al. (2020)[23]	III >1	172, pNET	Within the previous 12 months	G1 (13%) G2 (87%)	—	SSA (44%) ChT (26%) Everolimus (9%)	RCT: Surufatinib 300 mg daily Placebo	19 2	10.9[a] 3.7	—	Hypertension (38 vs 7), proteinuria (10 vs 2), hypertriglyceridemia (7 vs 0), diarrhea (4 vs 2)
Surufatinib	Dasari et al. (2023)	Ib/II >1	16 pNET 16 epNET	—	G1 and G2	—	—	Surufatinib 300 mg daily	18.8 pNET 6.3 EPNET	15.2 pNET 11.5 epNET		Fatigue (47), hypertension (44), proteinuria (38), diarrhea (34)

[a]Statistically significant.
[b]Difference is not statistically significant.
[c]Grade not specified.
[d]No *p*-value (non-comparative study).
[e]Including lung tumors.
[f]Pancreatic tumors cohort.
[g]Carcinoid tumors cohort.
BSC, best supportive care; ChT, chemotherapy; epNET, extra-pancreatic neuroendocrine tumor; G, grade; GEP, gastroenteropancreatic; GI, gastrointestinal; N, study population; NEC, neuroendocrine carcinoma; NEN, neuroendocrine neoplasms; NR, not reached; OS, median overall survival; pNET, pancreatic neuroendocrine tumors; PFS, median progression-free survival; PR, partial response; PRRT, peptide receptor radionuclide therapy; RCT, randomized clinical trial; SSA, somatostatin analog; TKI, tyrosine kinase inhibitors; —, not available.

Table 2. Summary of studies of gastrointestinal neuroendocrine tumors.

TKI	Study	Trial phase line	*N*, population	Previous progression	NEN grade	Ki-67 > 10% (%)	Previous systemic therapies	Design treatment arms	Response rate (%)	PFS (months)	OS (months)	Main drug-related grades 3–4 toxicities (%)
Pazopanib	Phan et al. (2015)[16]	II 1	32, pNEN; 20, carcinoid tumors[a] (11 small bowel)	Progressive disease (85% pNET and 66% carcinoid tumors)	G1 (75%) G2 (25%)	—	SSA (100%), Everolimus (25%[b] and 30%[c]), ChT (66%[b] and 25%[c])	Pazopanib 800 mg daily and depot octreotide	21.9 (pNEN) 0 (carcinoid tumors)	14.4 (pNEN) 12.2 (carcinoid tumors)	25 (pNEN) 18.5 (carcinoid tumors)	Hypertension (12), fatigue (8), diarrhea (6), neutropenia (6)
Pazopanib	Grande et al. (2015)[17]	II ⩾1	44 NET; 33 GEP (18 pancreas), 5 lung, and 3 thymic NET	Within the previous 12 months	G1 and G2	11	ChT (38%), TKI (36%), Everolimus (25%), SSA (80%)	Pazopanib 800 mg daily	9	9.5 (all population) 12.8 (pNET) 10 (GI NET) 3.4 (lung and thymic NETs)	—	Asthenia (16%), hepatotoxicity (16%), diarrhea (9%), hypertension (9%)
Pazopanib	Bergsland et al. (2019)[27]	II >1	171, GI NEN (113 small bowel)	Within the previous 12 months	G1 and G2	—	— (previous SSA mandate if midgut)	RCT: Pazopanib 800 mg daily vs Placebo (87% concurrent SSA)	—	11.6[d] 8.5	41.3 42.3	Hypertension (35 vs 8), fatigue (11 vs 4), diarrhea (7 vs 4), ALT (10 vs 0)
Cabozantinib	Chan et al. (2017)[28]	II >1	41, GI 20, pNET	Yes	G1 and G2	—	—	Cabozantinb 60 mg daily	15 GI 15 pNET	31.4 GI 21.8 pNET	—	Hypertension (13), hypophosphatemia (11), diarrhea (10), lymphopenia (7), fatigue (5)
Lenvatinib	Capdevila et al. (2021)[20]	II >1	55 pNET 56 GI NET	Within the previous 12 months	pNET: G1 (22%) G2 (76%) GI NET: G1 (38%) G2 (61%)	48 pNET 24 GI NET	SSA (86% pNET; 100% GI NET), everolimus (69% pNET), Sunitinib (29% pNET), ChT (32% pNET)	Lenvatinib 24 mg daily	44 pNET 16 GI NET	15.6 pNET 15.7 GI NET	32 pNET NR GI NET	Hypertension (22), fatigue (11), diarrhea (11), vomiting (8)

[a]Including lung tumors.
[b]Pancreatic tumors cohort.
[c]Carcinoid tumors cohort.
[d]Statistically significant.
ALT, alanine aminotransferase; ChT, chemotherapy; epNET, extra-pancreatic neuroendocrine tumor; G, grade; GEP, gastroenteropancreatic; GI, gastrointestinal; N, study population; NEN, neuroendocrine neoplasms; NR, not reached; OS, median overall survival; PFS, median progression-free survival; pNET, pancreatic neuroendocrine tumors; RCT, randomized clinical trial; SSA, somatostatin analog; TKI, tyrosine kinase inhibitors; —, not available.

compared with patients with pancreatic or GI NET ($p = 0.005$).[16]

In the phase III CABINET clinical trial of cabozantinib, 39 (19.8%) of the 197 patients with extrapancreatic NET had lung NET and analysis of this subgroup is planned.[24]

In an open-label basket phase II trial of cabozantinib plus atezolizumab in advanced and refractory NET, the ORR was zero in the cohort of nine patients with lung NET, and their median PFS was 8.4 months (95% confidence interval (CI): 7.7–NR).[27]

Patients with lung NET were included in clinical trials of lenvatinib, axitinib, surufatinib, nintedanib, and ibrutinib in non-pancreatic mixed NET but results of this subgroup are presented together with NET of distinct non-pancreatic sites of origin.[28–34]

Clinical trials reporting combined results of NET of distinct origins

Several TKI trials have reported combined outcomes for patients with different types of NETs, without discriminating results by primary sites (Table 3).

Sunitinib was evaluated in a single-arm trial in addition to hepatic arterial embolization in patients with GEP NET, reporting an objective RR of 72% and a median PFS of 15 months.[35] In a phase II trial of sunitinib in patients with G3 NET or NECs which progressed to chemotherapy, the observed RR was 14%, the median PFS was only 1.4 months, and the median OS was 6 months.[36]

Two phase II trials tested pazopanib in patients with G1–3 NET. The RR ranged from 18.9% to 24% and the overall disease-control rate was 63.5%–75.7%. In one of the trials, the median PFS was 9.1 months and OS was not reached at the time of analysis, while in the other, the median OS was 10.2 months.[14,17]

In the non-PanNET group of the CABINET trial,[24] the majority of tumors were G1/G2, 55% of patients had a small bowel NET and 19.8% had lung NET. The patients had received one or more previous treatment lines excluding a somatostatin analog: 67% had prior everolimus, 58% had received radioligand therapy, and 41% had chemotherapy. Cabozantinib increased the median PFS from 3.2 to 8.3 months (HR: 0.41; 95% CI: 027–0.62; $p < 0.0001$), with an overall RR of 4%. At a median follow-up time of 13.9 months, there was no difference in OS between the arms (21.9 and 22.4 months)—crossover was allowed after disease progression.

The combination of cabozantinib with atezolizumab was evaluated in an open-label phase II trial with six independent cohorts that included patients with various types of advanced endocrine tumors. In the cohort of GEPNET and extrapancreatic G3 NET, the RRs were, respectively, 16.7% and 0%, with median PFS of 13 and 2.7 months.[27]

The AXINET trial randomized 256 patients with G1/G2 advanced extra-pancreatic NET to receive octreotide LAR 30 mg monthly with axitinib (5 mg BID) or with placebo. Patients with small intestine (47%), lung (28%), rectum (6%), unknown primary (8%), gastric (3%), or colon (2%) NET were included. The patients could have received up to two previous lines of systemic treatment, but not prior VEGF or VEGFR-targeted drugs. By the blinded independent central review, the combination resulted in a significantly higher RR (13.2% vs 3.2%; $p = 0.0045$) and longer median PFS (16.6 vs 9.9 months; HR: 0.68; $p = 0.01$).[30]

A single-arm phase II trial evaluated the efficacy lenvatinib 18 mg/day combined with octreotide LAR 30 mg in second-line for patients with G1–G2 advanced non-pancreatic NET (50% had GI and 10% had lung NET). The overall RR was 41% and the median PFS was 19 months, although there was no information about baseline tumor progression.[28]

Surufatinib was investigated in Chinese patients with advanced extrapancreatic NET in a phase III placebo-controlled trial. The most common NET were GI (47%), unknown primaries (13.6%), thymic (12.6%), and lung (11.6%). The overall objective RR was 10% and the median PFS was 9.2 months in the surufatinib group versus 3.8 months in the placebo group (HR: 0.33; 95% CI: 0.22–0.50; $p < 0.0001$).[32]

Other TKIs (sorafenib, nintedanib, and ibrutinib) were evaluated in single-arm phase II trials and their results are summarized in Table 3.[33,34,37] A phase II trial of regorafenib combined with

Table 3. Summary of studies of NENs reported with different types combined.

TKI	Study	Trial phase line	*N*, population	Previous progression	NEN grade	Ki-67 > 10% (%)	Previous systemic therapies	Design treatment arms	Response rate (%)	PFS (months)	OS (months)	Main drug-related grades 3–4 toxicities (%)
Sunitinib	Strosberg et al. (2012)[37]	II ≥1	39, GEP NEN (26 small bowel, 9 pancreas)	Progressive disease (72%)	Low[a] (72%)	—	SSA (79%) ChT (15%)	Sunitinib 50 mg d1–28 q42d + bland hepatic artery embolization	72	15.2	NR	Neutropenia (15), hypertension (8), abdominal pain (8), diarrhea (5), fatigue (5)
Sunitinib	Pellat et al. (2018)[26]	II ≥1	31, GEP NEN (13 pancreas)	—	G3 NET (23%) NEC (77%)	100	ChT (90%)	Sunitinib 37.5 mg daily	13	1.4	6	Asthenia (26), hypertension (16), diarrhea (3)
Pazopanib	Ahn et al. (2013)[15]	II ≥1	37, GEP NEN (12 pancreases, 8 colorectums)	Within 3 months (81%)	G1 (22%), G2 (43%), G3 (35%)	—	None (51%) ChT (38%)	Pazopanib 800 mg daily	18.9	9.1	NR	Proteinuria (11), neutropenia (8), hypertension (5), diarrhea (5), abdominal pain (5)
Pazopanib	Katalinic et al. (2017)[18]	II	124, GEP NEN (85 pancreas)	—	G1 (48%) G2 (27%) G3 (25%)	—	—	Pazopanib 800 mg daily	24	At 6 months: 36%	10.2	Proteinuria (14), fatigue (12), neutropenia (11), diarrhea (7)
Cabozantinib	Chan et al. (2023)[25]	III ≥	197, epNET (109 GI NET and 39 lung NET) 93, pNET	Within the previous 12 months	EpNET: G1 (24%) G2 (64%) G3 (7%) pNET: G1 (20%) G2 (63%) G3 (10%)	—	EpNET: everolimus, (67%) Lu177 (58%), ChT (41%); pNET: everolimus (80%), Lu177 (56%), sunitinib (27%), ChT (61%)	RCT: Cabozantinib 60 mg daily Placebo	epNET (4 vs 1) pNET (18 vs 6)	epNET (8.3 vs 3.2)[h] pNET (11.4 vs 3)[h]	epNET (21.9 vs 22.4) pNET (43.5 vs 31)	Hypertension (27), fatigue (14), thromboembolic event (12), diarrhea (10), hand–foot syndrome (10)
Cabozantinib	Weber et al. (2023)	II >1	8 NET G3 12 NEC	Within the previous 9 months	G3	100	ChT (100%)	Cabozantinb 40 mg daily + Avelumab	25	4.7	15.5	Grade 3 (7): not specified
Cabozantinib	Capdevila et al. (2023)[29]	II >1	9 Lung NET, 24 G1–G2 GEP NEN, 9 G3 epNEN	Yes	G1, G2, and G3	—	—	Cabozantinb 40 mg daily + Atezolizumab	0 Lung NET, 16.7 G1–G2 GEP NEN, 0 G3 epNEN	8.4 Lung NET, 13 G1–G2 GEP NEN, 2.7 G3 epNEN	—	Fatigue (8), neutropenia (7), liver enzyme increase (7)
Lenvatinib	Goel et al. (2021)[30]	II >1	28 GI NEN, 6 Lung NEN, 22 others	—	G1 and G2	—	SSA (100%)	Lenvatinib 18 mg daily + Octreotide LAR 30 mg q4w	41	19	—	Fatigue (55), hypertension (32), diarrhea (29)
Axitinib	Strosberg et al. (2016)[31]	II	30, epNET (19 small bowel, 3 lung NET)	Within the previous 12 months	G1 and G2	—	—	Axitinib 5 mg twice daily	3[b]	26.7	45.3	Hypertension (63)

(Continued)

Table 3. (Continued)

TKI	Study	Trial phase line	*N*, population	Previous progression	NEN grade	Ki-67 > 10% (%)	Previous systemic therapies	Design treatment arms	Response rate (%)	PFS (months)	OS (months)	Main drug-related grades 3–4 toxicities (%)
Axitinib	Garcia-Carbonero (2021)[32]	II/III	256, epNET (120 small bowel, 72 lung NET)	Within the previous 12 months	G1 (29%) G2 (71%)	—	SSA (46%), everolimus (13%), ChT (13%)	RCT: Axitinib 5 mg twice daily + Octreotide LAR 30 mg q4w Placebo + Octreotide LAR	13.2 3.2[c]	16.6 9.9	—	Hypertension (21 vs 6), diarrhea (13 vs 1.5), asthenia (9 vs 3), nausea and vomiting (2 vs 0.7)
Regorafenib	Cousin et al. (2022)[38]	II >1	36 GEP NET 10 GEP NEC	—	G2 and G3	—	—	Regorafenib 160 mg daily + Avelumab	17 GEP NET 10 GEP NEC	5.5	NR	Hypertension (13), fatigue (13), diarrhea (11)
Surufatinib	Xu et al. (2019)[33]	Ib/II >1	42 pNET 39 epNET (14 rectum, 4 lung NET)	—	G1 (20%) G2 (80%)	—	SSA (52%) ChT (28%) TKI (22%) Everolimus (15%)	Surufatinib 300 mg daily	15 epNET[c]	21.2 pNET 13.4 epNET	—	Hypertension (33), proteinuria (12), hyperuricemia (10), diarrhea (6), hypertriglyceridemia (6)
Surufatinib	Xu et al. (2020)[34]	III >1	198, epNET (53 rectum, 23 lung, 25 thymic/ mediastinum NET)	Within the previous 12 months	G1 (16%) G2 (84%)	22	ChT (40%) SSA (32%) Everolimus (9%)	RCT: Surufatinib 300 mg daily Placebo	10[c] 0	9.2 3.8	—	Hypertension (36 vs 13), proteinuria (19 vs 0), anemia (7 vs 3)
Surufatinib	Dasari et al. (2023)	Ib/II >1	16 pNET 16 epNET	—	G1 and G2	—	—	Surufatinib 300 mg daily	18.8 pNET 6.3 EPNET	15.2 pNET 11.5 epNET	—	Fatigue (47), hypertension (44), proteinuria (38), diarrhea (34)
Sorafenib	Castellano et al. (2013)[39]	II 1–2	44, NET (13 pNET)	—	Well-differentiated[a]	—	75%	Sorafenib 200 mg twice daily + Bevacizumab 5 mg/kg q2w	9.8	12.4	—	Hand–foot skin reaction (16), asthenia (11), hypertension (9), mucositis (7)
Nintedanib	Iyer et al. (2020)[35]	II 1–2	32, epNET (13 small bowel, 7 colon, 4 lung NET)	Yes (84%)	Well-differentiated[a] (78%)	—	SSA (56%) Temozolomide (31%) Everolimus (22%)	Nintedanib 200 mg twice daily	3	11	32.7	Hypertension (19), nausea (3), diarrhea (3), fatigue (3)

[a]Grade not specified.
[b]Evaluable only for 22 patients.
[c]Statistically significant.
ChT, chemotherapy; epNET, extra-pancreatic neuroendocrine tumor; G, grade; GEP, gastroenteropancreatic; LAR: long acting release; N, study population; NEC, neuroendocrine carcinoma; NEN, neuroendocrine neoplasms; NR, not reached; OS, median overall survival; pNET, pancreatic neuroendocrine tumors; PFS, median progression-free survival; q4w, every 4 weeks; RCT, randomized clinical trial; SSA, somatostatin analog; TKI, tyrosine kinase inhibitors; —, not available.

avelumab in patients with GEP G2/G3 NET ($N=36$) or GEP NECs ($N=10$) reported a RR of 16.7% a median PFS of 5.5 months.

Discussion

This systematic review described the available data on TKIs in patients with advanced NET. Most studies were single-arm clinical trials, with a heterogeneous population in terms of primary tumor origins and the grade of NETs. Most studies evaluated TKIs in monotherapy. The outcome varied, depending on the TKI, primary tumor site, and associated therapy. Yet, placebo-controlled randomized clinical trials have demonstrated the efficacy of some TKIs.

TKIs demonstrated better outcomes in G1/G2 NET of pancreatic origin. In this context, four placebo-controlled phase III clinical trials (two with sunitinib, one with surufatinib, and one with cabozantinib) were performed, with objective RRs ranging from 9% to 20%, and median PFS times, from 9 to 21 months in patients with progressive tumors. Sunitinib is the only FDA-approved TKI in patients with NET, and it has been adopted as a treatment for patients with advanced/metastatic PanNET in second or further lines. A question that remains is how to sequence TKIs in patients with PanNET. Cabozantinib has been tested in patients whose NET had failed sunitinib, and this represented 29% of cases. RR and median PFS have not yet been reported for this subgroup but are planned.

In G1/G2 GI NETs, although the data about the efficacy of TKIs are heterogeneous, randomized placebo-controlled clinical trials have demonstrated antitumor activity with axitinib and cabozantinib in patients with progressing NET. Overall, RRs in G1/G2 GI NET were reported in 0–16%, of patients and median PFS times ranged from 8 to 16 months in patients with progressive disease. Notably, in these trials, GI NET is mostly represented by small bowel NET, with low proportions of patients with gastric or colorectal NET. Based on these findings, TKIs can be considered for patients with G1/G2 GI NET after disease progression on somatostatin analogs, radioligand therapy, and everolimus.

The role of TKIs in the treatment of patients with lung NET remains unknown. Clinical trials of TKIs have not been conducted specifically in patients with advanced lung NET. Yet, results from trials that included patients with lung NET patients have been reported combined with other types of NETs. A planned subgroup analysis of patients with lung NET from the CABINET trial is eagerly awaited to better inform on the efficacy of cabozantinib in this group. The evidence on the activity of TKIs in G3 NET is quite limited. In the CABINET trial, less than 10% of patients had a G3 NET, and the results of this subgroup have not been presented.

Toxicity from TKIs has been consistent with their use in other tumor types and did not seem to differ across patients with PanNET, GI NET, or lung NET. The main grade 3 or higher adverse events were hypertension, neutropenia, fatigue, diarrhea, and hand–foot skin reaction.[38]

This systematic analysis has some limitations. Most studies were not controlled, and several reported efficacy endpoints of different primary tumors jointly. Also, there was a low representation of NETs from lung, gastric, and colorectal origins, which compromises the interpretation of the efficacy of TKIs in these rare NETs.

Randomized clinical trials are necessary to determine the efficacy of TKIs in advanced NETs, and they were proven feasible to be conducted. This would account for known and unknown factors to avoid selection bias. Also, especially for slow-growing tumors, we think that radiological progression should require eligibility criteria to allow for a better assessment of antitumor activity. In that aspect, the most currently utilized efficacy endpoint of randomized trials in NET is PFS. Arguments in favor of PFS are that gains in OS depend on post-progression survival, which is difficult to measure in more indolent diseases such as NET where patients receive numerous post-progression treatments.[39]

Not least important, real-world data on TKIs are much needed to evaluate toxicity and efficacy according to dose intensity and to inform the outcomes of rare subgroups (e.g., colorectal primaries) and under-represented populations (e.g., elderly, Latin American, and African American patients).[40,41] Collaborative studies across countries are essential to fill such gaps.

Conclusion

In conclusion, TKIs have been effective in patients with advanced G1/G2 PanNET. In GI

NET, mostly represented by small bowel NET, axitinib and cabozantinib have been demonstrated to significantly improve RR and PFS. In patients with lung, gastric, or colorectal NET, the role of TKIs remains undetermined.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Author contributions
Rodrigo G. Taboada: Conceptualization; Data curation; Formal analysis; Methodology; Resources; Validation; Writing – original draft; Writing – review & editing.

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