Case Study Series

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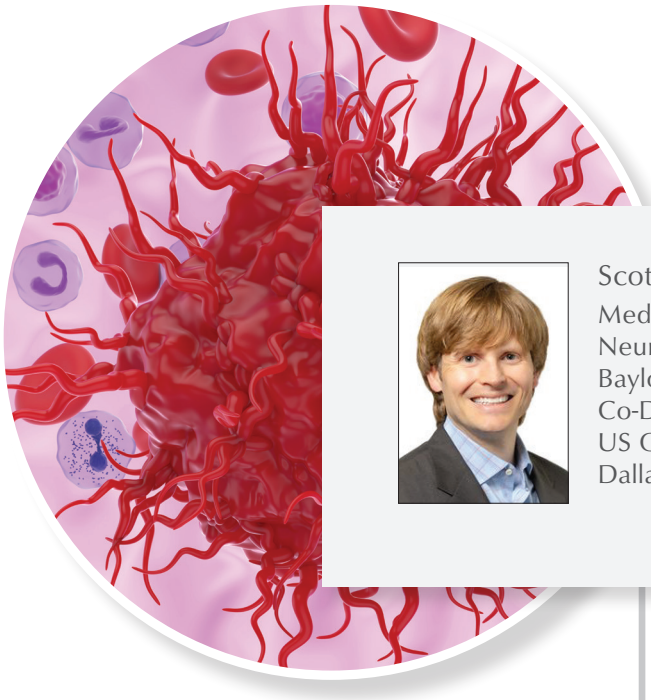
Modern Approaches in Neuroendocrine Tumors (NETs)



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In the Clinic: Case Studies

The following 2 patient cases highlight the clinical complexity of neuroendocrine tumors (NETs), and the widely different approaches in pancreatic NETs (pNETs) and extrapancreatic NETs (epNETs).

Patient 1: Female Patient With a Pancreatic NET

The patient has a long history of prior tumor diagnoses and resections, including a right hemicolectomy for stage 1 colon cancer associated with polyposis in 1984, a total abdominal hysterectomy for stage 1 uterine cancer determined to be associated with hereditary nonpolyposis colorectal cancer in 2004 (Muir-Torre syndrome with sebaceous carcinoma was subsequently identified), resection of a sebaceous carcinoma in 2016, and resection of squamous cell skin cancer in 2017.

A colonoscopy in April 2018 revealed two 3 mm tubular adenomatous polyps in the rectum and mid-transverse colon. Esophagogastroduodenoscopy demonstrated severe reflux esophagitis, a 1 cm hiatal hernia, nodular mucosa in gastric fundus and gastric body, extensive gastritis, and multiple nonbleeding postbulbar duodenal ulcers with biopsies negative apart from the presence of goblet cells. Her gastrin level was high (499 pg/mL), and rose in May 2018 from 589 pg/mL to 1590 pg/mL after secretin.

In May 2018, computed tomography (CT) of the abdomen and pelvis demonstrated a 2.9 cm pancreatic tail mass and 5.5 cm mass posterior to the pancreas, most consistent with lymphadenopathy. Additional lymphadenopathy was identified near the pancreas, along with numerous indeterminate liver lesions suspicious for metastases although some were consistent with cysts and gallstones. Prolactin, parathyroid hormone, and ionized calcium levels were normal.

The patient underwent endoscopic ultrasound and fine-needle aspiration. A biopsy of the primary pancreas lesion as well as a peripancreatic lymph node demonstrated a well-differentiated NET, with Ki-67 expression scored as 4% to 6%, consistent with an intermediate grade (grade 2). Testing showed the tumor to be high for both microsatellite instability (MSI) and tumor mutational burden.

The patient started treatment with a somatostatin analogue. Multiple subsequent CT scans revealed slight interval changes, until in July 2019 a CT scan demonstrated interval millimetric progression.

The patient switched to treatment with ^{177}Lu-Dotatate, completing 4 cycles in February 2020. A CT scan in

On the Cover
Illustration of a neuroendocrine tumor cell.

Credit: Nemes Laszlo / Science Source

September 2021 demonstrated interval slight progression in the liver and stability of the pancreas lesions. At this point she was enrolled in a clinical trial evaluating surufatinib. However, in early December 2021, the patient was admitted to the emergency department for hypertensive crisis. She discontinued surufatinib but continued treatment with octreotide long-acting release (LAR).

In June 2022, the patient started treatment with capecitabine plus temozolomide. In October 2022, capecitabine was stopped, but single-agent temozolomide continued. A repeat CT-guided biopsy of the liver lesion in November 2022 demonstrated persistent intermediate grade NET. Stable disease continued for the next year. In June 2023 her gastrin level was found to have increased to 717 pg/mL from 554 pg/mL in April 2023 but a CT scan in September 2023 revealed that the large mass within the anterior pararenal space was unchanged in size.

In April 2024, the patient started treatment with pembrolizumab. Subsequent imaging suggested disease progression at 3 months, although this was thought possibly owing to pseudoprogression. She stopped pembrolizumab and initiated everolimus in July 2024. After 6 weeks of treatment, she developed severe pneumonitis and stopped everolimus. Several months later, she started to develop symptomatic hypoglycemia and her workup was consistent with clear insulin production from preexisting tumors. A retrial of pembrolizumab from December 2024 to February 2025 was met with disease progression. The tumor now appeared to be secreting both high levels of gastrin and insulin (required diazoxide).

In February 2025, the patient started treatment with cabozantinib.

Patient 2: Male Patient With a Lung NET

An otherwise healthy African-American male experienced episodes of fatigue and lightheadedness after going on a cruise in April 2013. Evaluation by his primary care physician revealed an abnormal chest radiograph. A chest CT scan was suggestive of a multilobulated mass in the right hilum and right upper lung and right mid lung. Mass effect was evident, with distortion of the right pulmonary artery and mediastinum, and a narrowed superior vena cava. Some mediastinal lymph nodes were positive, and a mild adrenal thickening suggestive of hypoplasia was noted. The right upper lobe of the lung, the right mainstem bronchus, and the right mid-lung bronchus were all narrowed.

Biopsy of the right upper lung lesion revealed a right lung mass suggestive of neuroendocrine carcinoma grade 1; the overall morphology was compatible with a grade 1 NET with Ki-67 of less than 1% with less than 1 mitosis per high-power field. The tumor was positive for synaptophysin and chromogranin, but negative for thyroid transcription factor 1. These findings indicated a classic carcinoid-based tumor.

Table 1. 5-Year Overall Survival Patients With Localized, Regional, and Metastatic pNETs: SEER Database Analysis

pNETs		5-year overall survival, %
Localized	**Overall**	**83.19**
	Grade 1	87.28
	Grade 2	79.69
	Grade 3	46.24
Regional	**Overall**	**67.36**
	Grade 1	80.99
	Grade 2	72.49
	Grade 3	38.19
Metastatic	**Overall**	**28.13**
	Grade 1	51.03
	Grade 2	45.16
	Grade 3	12.37

pNETs, pancreatic neuroendocrine tumors; SEER, Surveillance, Epidemiology, and End Results. Adapted from Sonbol MB et al. *Oncologist*. 2022;27(7):573-578.[8]

Initial workup did not indicate evidence of significant serotonin production. The positron emission tomography (PET)/CT scan showed mild activity in the right hilum and right pulmonary region with mass measuring 3.7 × 3.2 × 3.0 cm in this area and a separate mass in the right upper lung, measured at 3.6 × 3.1 × 2.5 cm with a standardized uptake value activity scored at 2.8. These findings were considered consistent with evidence of an underlying malignancy. A few tiny nodules in the right upper lung (8.0 × 7.0 mm with no abnormal uptake) were too small to be characterized by PET scan. The soft tissues of the chest showed no abnormal uptake, and the abdomen and pelvis also showed no overt evidence of any other sites of uptake. The right upper lung opacities were suggestive of the underlying malignancy. A follow-up octreotide scan and a ^{68}Ga-Dotatate PET/CT scan demonstrated hepatic metastases.

Treatment was initiated with octreotide 30 mg monthly, and when he showed signs of disease progression, treatment was changed to everolimus. Upon disease progression after 6 months, he received ^{177}Lu-Dotatate, and again after disease progression started a surufatinib clinical study in November 2021.

CT imaging in June 2023 showed progression in the right hepatic lobe, with an approximately 2 cm increase

in the right lobe lesion. The patient developed refractory diarrhea, and a 5-hydroxyindoleacetic acid (5-HIAA) test was 270 mg/24 hours (previously normal but not routinely checked). The patient then underwent bland embolization to the dominant right hepatic lobe lesion, complicated by severe postembolization syndrome with malaise and fatigue.

CT imaging in August 2023 demonstrated stability of nonembolized lesions, as well as postembolization effects and the embolized lesion without evidence of infection.

In November 2023, a CT scan of the chest, abdomen, and pelvis demonstrated overall improvement in the volume of tumor in the hepatic lesions. In April 2024, a CT scan of the chest, abdomen, and pelvis demonstrated improvement in some of the liver metastases postembolization and progression in some of the untreated lesions. A new 1.8 cm lesion in the caudate lobe was observed. A left ischium bone metastasis, present since at least 2021, continued to be present.

The patient started cabozantinib in February 2025.

Overview of NETs

Neuroendocrine neoplasms (NENs), a group of heterogeneous malignancies arising from neuroendocrine cells, describe cancers that can be further classified based on their histology into NETs and neuroendocrine carcinomas (NECs).[1] NETs are well-differentiated NENs generally categorized as grade 1 (low), grade 2 (intermediate), or grade 3 (high) based on proliferation rates.[1,2]

NETs are also classified clinically by their anatomic location, as that dictates their management.[1,3] NETs may be classified as foregut, midgut, and hindgut based on embryonic divisions of the digestive tract. Additionally, NETs are frequently referred to as either pNETs, if they arise in the tissues of the pancreas, or as epNETs, if they arise in tissues outside the pancreas (eg, lung, gastrointestinal [GI] tract). Some clinical trials have grouped NETs involving the GI tract and the pancreas together, referring to them as gastroenteropancreatic NETs (GEP-NETs).[4]

Although NETs may arise from any organ, they are most frequently diagnosed in the GI tract, lung, and pancreas.[5-7] In fact, about one-half of all NETs arise in the GI tract, involving the large intestine (23%), small intestine (18%), stomach (7%), and appendix (5%); followed by lungs (25%) and pancreas (8%). NETs arising in the thyroid, thymus, breast, and skin are rare.

Although NETs are rare tumors with an estimated 12,000 new cases diagnosed annually,[5] their incidence appears to be increasing.[8] Many NETs are asymptomatic at diagnosis and are found only incidentally. When symptoms of a NET do occur, they often vary based on the tumor location and the types of hormones secreted by the NET cells. These types of NETs, which produce and secrete hormones, are referred to as functional NETs and account for about 40% of all NETs. Classically, functional NETs can cause carcinoid syndrome upon overproduction of serotonin and other signaling molecules.

The prognosis of patients with NETs varies widely, depending on the grade, stage, and site of origin. Table 1 shows that the 5-year overall survival rates for patients with pNETs decreases with advancing disease stage and grade.[8] Across all NETs, the median overall survival is 9.3 years, although this ranges from several decades for patients diagnosed with localized NETs to approximately 12 months in the case of metastatic NETs.[9] As they progress, the most common site of NET metastasis is the liver, although other sites may include the lung, bone, lymph nodes, and central nervous system.[10]

FDA-approved Treatment Options (1998–2024) and the Unmet Need in NETs

The treatment of NETs can be broadly classified into 2 categories—surgery/localized therapies and systemic therapies—which are used to achieve different goals.[1] The role of surgery and localized therapies in advanced or metastatic NETs is primarily debulking, as they are typically used to treat the most common site of metastases: the liver. In contrast, systemic therapies are widely used to achieve both symptomatic control as well as improved survival (Table 2).[11-24]

Somatostatin Analogues (SSAs)

Considered a first-line therapy in the treatment of NETs, somatostatin analogues (SSAs) are synthetic versions of the natural hormone somatostatin that act to inhibit the secretion of various hormones (including serotonin, insulin, glucagon, and gastrin).[25,26] SSAs work by binding to and occupying their target somatostatin receptors (SSTRs), expressed on the cell surface of some NETs. For example, SSTR expression is high in pNETs (approaching 80%-90%), although it is lower in other NETs.[27,28] There are 5 types of SSTRs (termed SSTR1-5), with SSTR2 being the most frequently expressed.[26]

SSAs were initially developed to reduce symptoms in patients with functional NETs via inhibition of hormone secretion. However, their additional antitumor effect, both direct and indirect, on NET cells was subsequently discovered.[29,30]

Two SSAs are used in the treatment of patients with NETs: octreotide (used as an LAR formulation approved by the US Food and Drug Administration [FDA] in 1998) and lanreotide (FDA approved in 2014).[11,14] Octreotide LAR is an even more potent inhibitor of

Table 2. FDA-approved Treatment Options for NETs (1998-2024)

Drug classes/ agent	FDA approval	Pivotal trial	Primary endpoint
SSA			
Octreotide LAR	1998[11]	PROMID[12,13] 85 patients with locally inoperable or metastatic, well-differentiated midgut NETs	*Primary endpoint* Median TTP: 14.3 months vs 6.0 months with placebo; HR, 0.34; 95% CI, 0.20-0.59; *P*=.000072 *Secondary endpoint* Median OS: 84.7 months vs 83.7 months with placebo; HR, 0.83; 95% CI, 0.47-1.46
Lanreotide	2014[14]	CLARINET[15] 204 patients with nonfunctioning, unresectable, well- or moderately differentiated, metastatic or locally advanced SSTR-positive GEP-NETs with Ki-67 values <10%	*Primary endpoint* Median PFS: 33.4 months vs 18.0 months with placebo; HR, 0.47; 95% CI, 0.30-0.73; *P*<.001 *Secondary endpoint* Median TTP: not reached vs 18.0 months with placebo; *P*<.001
PRRT			
^{177}Lu-Dotatate	2018[16]	NETTER-1[17] 229 patients with progressive, well-differentiated (grade 1 or 2) SSTR-positive midgut GEP-NETs that had progressed on treatment with octreotide LAR	*Primary endpoint* Median PFS: not reached vs 8.4 months with octreotide LAR; HR, 0.21; 95% CI, 0.13-0.33; *P*<.001 *Secondary endpoint* Median OS: 48.0 months vs 36.3 months with placebo; HR, 0.84; 95% CI, 0.60-1.17; *P*=.30
		NETTER-2[18] 226 patients with newly diagnosed advanced, well-differentiated (grade 2 or 3) GEP-NETs	*Primary endpoint* Median PFS: 22.8 months vs 8.5 months with octreotide LAR; stratified HR, 0.276; 95% CI, 0.182-0.418; *P*<.0001 *Secondary endpoint* Median OS data immature at time of primary analysis
Targeted agents			
Everolimus	2011 (pNETs); expanded to progressive, nonfunctional GI and lung NETs in 2016[19]	RADIANT-3[20,21] 410 patients with locally advanced or metastatic pNETs	*Primary endpoint* Median PFS: 11.0 months vs 4.6 months with placebo; HR, 0.35; 95% CI, 0.27-0.45; *P*<.001 *Secondary endpoint* Median OS: 44.0 months vs 37.7 months with placebo; HR, 0.94; 95% CI, 0.7-1.2; *P*=.30
		RADIANT-4[22] 302 patients with unresectable, locally advanced or metastatic, well-differentiated (low or intermediate grade), nonfunctional NETs of GI (excluding pancreatic) or lung origin	*Primary endpoint* Median PFS: 11.0 months vs 3.9 months with placebo; HR, 0.48; 95% CI, 0.35-0.67; *P*<.00001 *Secondary endpoint* Median OS: HR, 0.64; 95% CI, 0.40-1.05; one-sided *P*=.037 [boundary for statistical significance was .0002])
Sunitinib	2011[23]	SUN-1111[24] 171 patients with advanced and/or metastatic pNETs	*Primary endpoint* Median PFS: 11.4 months vs 5.5 months with placebo; HR, 0.42; 95% CI, 0.26-0.66; *P*<.001 *Secondary endpoint* Median OS: not estimable in either arm; HR, 0.41; 95% CI, 0.19-0.89; *P*=.02

FDA, US Food and Drug Administration; GEP-NETs, gastroenteropancreatic neuroendocrine tumors; GI, gastrointestinal; HR, hazard ratio; NETs, neuroendocrine tumors; OS, overall survival; PFS, progression-free survival; pNETs, pancreatic neuroendocrine tumors; PRRT, peptide receptor radionuclide therapy; SSA, somatostatin analogue; TTP, time to tumor progression.

Table 3. Outcomes With Cabozantinib vs Placebo in the CABINET Study

Outcome	Patients with epNETs		Patients with pNETs	
	Cabozantinib (n=134)	Placebo (n=69)	Cabozantinib (n=64)	Placebo (n=31)
Median PFS,[a] months (95% CI)	8.4 (7.6-12.7)	3.9 (3.0-5.7)	13.8 (9.2-18.5)	4.4 (3.0-5.9)
Stratified HR (95% CI)	0.38 (0.25-0.59) log-rank *P*<.001		0.23 (0.12-0.42) log-rank *P*<.001	
ORR,[b] %	5	0	19	0

epNETs, extrapancreatic neuroendocrine tumors; HR, hazard ratio; ORR, objective response rate; PFS, progression-free survival; pNETs, pancreatic neuroendocrine tumors.

[a]According to the updated analysis in the latest cabozantinib prescribing information (March 26, 2025), PFS in the epNET cohort was 8.5 months (cabozantinib) vs 4.2 months (placebo) (HR [95% CI], 0.40 [0.26, 0.61]) and in the pNET cohort was 13.8 months (cabozantinib) vs 3.3 months (placebo) (HR [95% CI], 0.22 [0.12, 0.41]).

[b]According to the updated analysis in the latest cabozantinib prescribing information (March 26, 2025), the ORR in the pNET cohort was 18% (cabozantinib) vs 0% (placebo).

Adapted from Chan JA et al. *N Engl J Med*. 2025;392(7):653-665.[39]

hormone release than somatostatin. Although octreotide is FDA approved for hormone control, lanreotide is approved to achieve both hormone control and tumor control of NETs; however, in clinical practice both SSAs are used interchangeably.[1,12-15] Common adverse effects associated with SSAs include nausea, abdominal cramping, diarrhea, steatorrhea, flatulence, and hyperglycemia. In general, these effects are mild and usually resolve rapidly and spontaneously.[1]

Peptide Receptor Radionuclide Therapy (PRRT)

Another form of systemic treatment for NETs is peptide receptor radionuclide therapy (PRRT), which is used to target radiotherapy directly to the site of a NET.[30] The PRRT agent ^{177}Lu-Dotatate, approved by the FDA in 2018, combines a lutetium radionuclide with an SSA and is indicated for adult and pediatric patients 12 years and older with SSTR-positive GEP-NETs, including foregut, midgut, and hindgut NETs.[16,17,31,32] Mild toxicities related to PRRT include nausea, abdominal pain, asthenia, and hair loss.[18] Additionally, there is a potential for severe toxicities with ^{177}Lu-Dotatate, especially affecting the bone marrow and the kidneys. ^{177}Lu-Dotatate–induced damage to the bone marrow can result in hematologic toxicity. Although generally mild, severe neutropenia and thrombocytopenia may occur. In addition, secondary malignancies such as myelodysplastic syndrome and acute myeloid leukemia may occur and have been reported. Renal toxicity may occur resulting from the high expression of SSTR in the kidney combined with a renal excretion route for ^{177}Lu-Dotatate. As a result, an amino acid solution is recommended before, during, and after ^{177}Lu-Dotatate administration to reduce the amount of reabsorption of the radionuclide into the kidneys.

Targeted Agents

Until 2024, only 2 targeted agents were approved for the treatment of NETs: everolimus and sunitinib.[19,23] The rapamycin analogue everolimus was approved by the FDA in 2011 for pNETs, and in 2016 its indication was expanded to included progressive, nonfunctional GI and lung NETs. It is a small molecule inhibitor of the mammalian target of rapamycin, a protein that lies downstream of the PI3K/Akt signaling pathway, which has a critical role in cancer cell growth and the pathogenesis of NETs.[33] Everolimus has 2 FDA-approved indications for NETs: first for the treatment of adult patients with progressive pNETs with unresectable, locally advanced or metastatic disease, and second for the treatment of adult patients with progressive, well-differentiated, nonfunctional NETs of GI or lung origin with unresectable, locally advanced or metastatic disease.[19-22] Overall adverse effects associated with everolimus include stomatitis, rash, fatigue, infection, pulmonary toxicities, hyperglycemia, anemia, and thrombocytopenia. Although primarily mild, some toxicities can be severe (particularly stomatitis).[26]

Sunitinib, approved by the FDA in 2011, is a multitargeted tyrosine kinase inhibitor (TKI) known to act against a range of receptor tyrosine kinases (RTKs), some of which are involved in intracellular pathways implicated in tumor growth, angiogenesis, and metastatic progression of cancer.[26] The FDA approval of sunitinib in NETs is limited to the treatment of progressive, well-differentiated pNETs in adult patients with unresectable locally advanced or metastatic disease.[23,24] Most adverse reactions reported with sunitinib are mild and GI-related

Table 4. Selected Grade 3 or 4 AEs Reported With Cabozantinib vs Placebo in the CABINET Study

Grade 3/4 AE	Patients with epNETs, %		Patients with pNETs, %	
	Cabozantinib (n=132)	Placebo (n=67)	Cabozantinib (n=63)	Placebo (n=31)
Any	62	27	65	23
Fatigue	13	7	11	3
Diarrhea	11	4	6	0
Hypertension	21	3	22	10
Mucositis	4	0	8	0
PPE	3	0	10	0
VTE	0	0	11	0

AE, adverse event; epNETs, extrapancreatic neuroendocrine tumors; pNETs, pancreatic neuroendocrine tumors; PPE, palmar-plantar erythrodysesthesia; VTE, venous thromboembolism.
Adapted from Chan JA et al. *N Engl J Med*. 2025;392(7):653-665.[39]

(diarrhea, stomatitis, nausea, abdominal pain, and vomiting), although asthenia and fatigue may also occur.[26] In some cases, toxicities may be severe.

Unmet Need

Although several agents are available for the treatment of patients with NETs, there remains an unmet need for patients who progress on existing therapies. Only 1 new treatment option (^{177}Lu-Dotatate) has received FDA approval in the past decade, and the only 2 targeted agents for NETs were approved up until 2024.

Cabozantinib: The Newest Addition to the Oncologist's Toolkit

Studies suggest that angiogenesis has an important role in the pathogenesis of NETs.[34,35] Thus agents targeting vascular endothelial growth factor and its receptor have been explored as a novel treatment for these tumors. One such agent is cabozantinib, an oral TKI known to inhibit multiple RTKs involved in angiogenesis and tumor progression.[36]

Cabozantinib is indicated as a treatment for multiple tumor types, including advanced renal cell carcinoma, previously treated hepatocellular carcinoma, and advanced or metastatic differentiated thyroid cancer.[37] On March 26, 2025, the FDA approved cabozantinib as a treatment for adult and pediatric patients 12 years or older with previously treated, unresectable or locally advanced or metastatic, well-differentiated pNETs and epNETs.

CABINET Study

Cabozantinib was initially investigated as a novel therapy for patients with NETs in a phase 2 trial with promising results.[38] This led to the design and conduct of the CABINET study, a randomized, double-blinded, placebo-controlled, phase 3 study to determine the efficacy and safety of cabozantinib in patients with previously treated, progressive epNETs or pNETs.[39]

Enrolled patients with epNETs or pNETs were grouped into 2 independent cohorts, and within each cohort were randomized in a 2:1 ratio to treatment with either cabozantinib 60 mg or placebo, both administered orally once daily. Treatment was continued until disease progression, unacceptable toxicity, or consent withdrawal. Following a protocol amendment, patients in the placebo arm were permitted to cross over to receive open-label cabozantinib after central confirmation of disease progression. At the time of randomization, patients in the epNET cohort were stratified by concurrent SSA use and primary tumor site (midgut GI and unknown primary vs non-midgut Gl, lung, other sites). In the pNET cohort, patients were stratified by concurrent SSA use and prior receipt of sunitinib.

Based on guidance from the National Cancer Institute,[40,41] the primary endpoint for this phase 3 trial of a novel systemic therapy in NETs was progression-free survival per blinded independent central review. Secondary endpoints included confirmed objective response rate, overall survival, and safety.

A total of 298 patients enrolled in the CABINET study between October 2018 and August 2023 were placed in either the epNET cohort (n=203) or the pNET cohort (n=95).[39] The intention-to-treat cohorts included 7 patients with pNETs who were mistakenly entered into the epNET cohort and 3 patients with epNETs who were mistakenly entered into the pNET cohort. Note that this has since been corrected and the latest cabozantinib prescribing information (March 26, 2025) contains updated analysis of these patient cohorts.[37]

CABINET: Outcomes in the epNET Cohort

After a median follow-up of 10.2 months in the epNET cohort, the median progression-free survival was 8.4 months with cabozantinib and 3.9 months with placebo (Table 3). Thus, cabozantinib was associated with a 62% lower risk of disease progression or death compared with placebo (stratified hazard ratio [HR], 0.38; 95% CI, 0.25-0.59; *P*<.001). The updated analysis in the cabozantinib prescribing information states the progression-free survival as 8.5 months (cabozantinib) versus 4.2 months (placebo).

The benefit in progression-free survival was observed across several patient subgroups evaluated. Median overall survival appeared to be prolonged among cabozantinib-treated patients as compared with placebo-treated patients (21.9 vs 19.7 months, respectively; HR, 0.86; 95% CI, 0.56-1.31); median follow-up time for survival was 24.2 months. Note that the updated analysis in the cabozantinib prescribing information states that the overall survival data were not mature. The objective response rate was 5% (95% CI, 2-10) with cabozantinib versus 0% (95% CI, 0-5) with placebo (*P*=.05); all responses were partial responses.

Grade 3 or higher adverse events were more frequent with cabozantinib (62%) versus placebo (27%). The most common treatment-related grade 3 or 4 adverse events (Table 4) with cabozantinib were hypertension (21%), fatigue (13%), and diarrhea (11%). A similar percentage of patients in each arm experienced a grade 5 event, primarily attributed to underlying disease (7% with cabozantinib vs 6% with placebo). Two-thirds of patients in the cabozantinib arm underwent a dose reduction (66%) compared with 10% of patients in the placebo arm. The rate of treatment discontinuation owing to adverse events was about twice as high with cabozantinib versus placebo (31% vs 15%).

CABINET: Outcomes in the pNET Cohort

After a median follow-up of 13.8 months in the pNET cohort, the median progression-free survival was 13.8 months and 4.4 months in the cabozantinib and placebo arms (Table 3), respectively—a 77% lower risk of disease progression or death with cabozantinib compared with placebo (stratified HR, 0.23; 95% CI, 0.12-0.42; *P*<.001). The updated analysis in the cabozantinib prescribing information states the progression-free survival as 13.8 months (cabozantinib) versus 3.3 months (placebo).

This benefit in progression-free survival was observed across multiple subgroups tested. After a median follow-up of 23.1 months for overall survival, median overall survival was 40 months with cabozantinib versus 31.1 months with placebo (HR, 0.95; 95% CI, 0.45-2.00). Note that the updated analysis in the cabozantinib prescribing information states that the overall survival data were not mature. The objective response rate was 19% (95% CI, 10-30) with cabozantinib and 0% (95% CI, 0-11) with placebo (*P*=.01); all responses were partial responses. The updated analysis in the cabozantinib prescribing information states that the objective response rate was 18% (cabozantinib) versus 0% (placebo).

Grade 3 or higher adverse events were also more frequent with cabozantinib (65%) versus placebo (23%). The most common treatment-related grade 3 or 4 adverse events (Table 4) with cabozantinib were hypertension (22%), fatigue (11%), and thromboembolic events (11%). No grade 5 events were reported in the pNET cohort. Dose reductions were required in 68% of patients in the cabozantinib arm compared with 19% of patients in the placebo arm. The rate of treatment discontinuation owing to adverse events was 20% with cabozantinib; no patients in the placebo arm discontinued treatment.

CABINET: Subgroup Analysis

A subgroup analysis of the CABINET study, which focused on outcomes in patients with a primary NET arising in the GI tract, has been reported.[42] Among the 116 patients included in this subgroup analysis, 70 were treated with cabozantinib and 46 with placebo. The outcomes in this subgroup (Table 5) demonstrated the significant benefit of cabozantinib in this population of patients. The benefit in progression-free survival with cabozantinib observed in the overall subgroup population was also seen across multiple patient subgroups, including across clinical factors such as tumor grade and functional status and across prior and concurrent treatment history.

Cabozantinib in Clinical Practice

The CABINET study demonstrated significantly improved progression-free survival with cabozantinib in patients with heavily pretreated, progressive and advanced pNETs and epNETs including lung NETs. CABINET was also the first phase 3 trial to classify patients into different treatment cohorts by site of NET origin.

The broad recruitment of patients with grade 1 through grade 3 NETs as well as NETs from any site of origin, along with the oral administration of cabozantinib—allowing for greater control, including dose modifications to manage adverse events—provides support for the addition of cabozantinib to the oncologist's toolkit for wide use in the NET patient population. This brings to the forefront the question of where cabozantinib should be placed within the treatment landscape for NETs.

Table 5. Outcomes With Cabozantinib vs Placebo for Advanced Gastrointestinal NETs After Progression on Prior Therapy: Subgroup Analysis of the Phase 3 CABINET Study (Alliance A021602)

Outcome		Cabozantinib (n=70)	Placebo (n=46)	HR (95% CI)
Progression-free survival				
Median (95% CI), months		8.5 (6.0-16.7)	5.6 (3.9-11.0)	0.50 (0.28-0.88); 1-sided stratified log-rank *P*=.007
Subgroup		**Events/N**	**Events/N**	**HR (95% CI)**
Grade	**1**	16/28	10/13	0.30 (0.13-0.68)
	2	18/38	12/28	0.66 (0.31-1.40)
	3	3/3	3/4	0.74 (0.15-3.71)
Concurrent SSA	**No**	3/9	5/9	0.41 (0.09-1.76)
	Yes	34/61	21/37	0.52 (0.29-0.92)
Prior everolimus	**No**	16/27	12/21	0.57 (0.26-1.22)
	Yes	21/43	14/25	0.42 (0.20-0.85)
Prior ^{177}Lu-Dotatate	**No**	5/15	6/12	0.19 (0.05-0.71)
	Yes	32/55	20/34	0.58 (0.33-1.04)
Functional status	**Functional**	19/33	12/20	0.43 (0.20-0.91)
	Non-functional	12/24	10/17	0.42 (0.18-1.02)
	Unknown	6/13	4/9	0.81 (0.23-2.87)
Best overall response (RECIST v1.1) by BICR, n (%)				
Partial response		1 (1)	0	
Stable disease		48 (69)	30 (65)	
Progressive disease		6 (9)	12 (26)	
Not evaluable		15 (21)	4 (9)	

BICR, blinded independent central review; HR, hazard ratio; NET, neuroendocrine tumor; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SSA, somatostatin analogue. Adapted from Strosberg JR et al. *J Clin Oncol*. 2025;43(4)(suppl):666-666.[42]

Given the strong data of cabozantinib improving progression-free survival across a broad range of NETs, clinicians may elect to use cabozantinib before everolimus. Cabozantinib may also have a role in patients who are not candidates for ^{177}Lu-Dotatate for reasons such as kidney dysfunction, lack of receptor expression, or an extremely small burden of disease.

Cabozantinib was approved by the FDA in advanced NETs on March 26, 2025. It is also included in the NET treatment algorithms of the recently updated National Comprehensive Cancer Network (NCCN) guidelines.[43] Cabozantinib is recommended as a category 2A treatment option for patients with locally advanced or metastatic epNETs including those arising in the GI tract, lung, or thymus, and also in patients with locoregionally advanced or metastatic pNETs. Cabozantinib is considered a category 1 recommendation in these patients if they have received prior everolimus, ^{177}Lu-Dotatate (in the case of GI tumors), or sunitinib (in patients with pNET).

Modern Approach to Management of pNETs

In pNETs, the NCCN guidelines list 6 preferred regimens: cabozantinib (category 1 if prior treatment with everolimus, ^{177}Lu-Dotatate, or sunitinib); everolimus (category 1 for progressive disease); sunitinib (category 1 for progressive disease); octreotide LAR or lanreotide (if SSTR-positive); ^{177}Lu-Dotatate (if SSTR-positive and progression on octreotide LAR or lanreotide); or temozolomide plus capecitabine (preferred when tumor response is needed for symptoms or cytoreduction). However, the NCCN guidelines also state that there are no data to support a specific sequence of regional versus systemic therapy and no data to guide sequencing of the recommended systemic therapy options.[43] The CABINET study suggests that cabozantinib is effective after everolimus, ^{177}Lu-Dotatate, or sunitinib.

For patients with bulky, higher-grade disease, I tend to use a PRRT-based regimen as an initial treatment, as

I do not have to worry about tumor-induced flares or radiation deposition. Patient preference must also be considered in decision-making. Many patients I see are very suspicious of injecting radiation into their veins. This alone may often push ^{177}Lu-Dotatate treatment later in the line of therapies. Also, patients who have been pretreated with Yttrium-90 have already been exposed to a fairly high burden of radiation. For such patients as well, I tend to push ^{177}Lu-Dotatate to the end of the treatment algorithm. ^{177}Lu-Dotatate will likely be preferred in patients with bulky pNETs who need a rapid response and decrease in tumor size. However, for patients with less bulky disease, ^{177}Lu-Dotatate may not be the first choice, given its significant side effect profile.

In terms of sequencing targeted therapy in general, everolimus will remain widely used, but clinicians may begin to prefer cabozantinib because of its tolerability. Although the efficacy of sunitinib in pNETs has been demonstrated since 2011, sunitinib appears to have fallen out of favor with many community oncologists because of its adverse event profile, and therefore features later in sequencing.

My use of cabozantinib will depend on tumor characteristics such as the degree of bulkiness as well as the strength of the uptake of PRRT, and patient characteristics such as clinical trial options, whether patients can access clinical studies or they live in a remote area, and if patients are being treated by telemedicine with the assistance of a specialty pharmacy. Logistics is a major consideration when there is no clear medical pathway, such as is the case in pNETs, and both patient and physician preferences are considered, rather than using a very rigid decision-making process.

Modern Approach to Management of Lung NETs

The NCCN guidelines in NETs include the following treatment recommendations for lung NETs: cabozantinib (category 1 if prior treatment with everolimus); everolimus (category 1 for nonfunctional lung NETs); and octreotide LAR or lanreotide (if SSTR-positive and/or with hormonal symptoms).[43] Here, too, the NCCN guidelines state there are currently no data to support a specific sequence of regional versus systemic therapy and no data to guide sequencing of the recommended systemic therapy options.

In lung NETs, substantial data demonstrate the efficacy of everolimus and cabozantinib; data on SSA therapy in lung NETs are modest, as these clinical studies in lung NETs were slow to accrue and were stopped. SSA therapy can have significant activity in patients whose tumors are strongly SSTR-positive on PET, but these data are scant. PRRT with ^{177}Lu-Dotatate is utilized probably a little more than it should be in this tumor type, as lung NETs are often poorly SSTR-positive. There are still many patients who are initially treated with carboplatin plus etoposide. Only recently have clinicians started to question whether platinum-etoposide chemotherapy is beneficial for patients with low-grade NETs.[44-46]

Back to the Clinic

Patient 1: Female Patient With a Pancreatic NET

When this patient was being treated with pembrolizumab, she started developing refractory hypoglycemia. After heavy pretreatment with radiation and alkylator-based therapy, she had markedly elevated proinsulin and insulin levels, all consistent with a newly insulin-producing tumor. One fascinating part of this case is that, despite showing MSI-high status, the tumor demonstrated absolutely no response to immunotherapy. The patient was subsequently started on cabozantinib. Her initial 60 mg dosing was held owing to mucositis.

Patient 2: Male Patient With a Lung NET

The second patient was diagnosed in 2013 with a fairly large lung NET. His right lung was beginning to cause some narrowing of the bronchus and superior vena cava, and a good deal of highly symptomatic local disease from a well-differentiated NET of the lung. What is interesting about this case is that he had been labeled as having a nonfunctional tumor, yet started developing significant diarrhea and was found to have an extremely high 5-HIAA (over 300 mg/24 hours). However, his 5-HIAA levels had not been routinely checked. He may have had some sort of migration of secretary production after an extremely prolonged treatment course. He was on a double dose of SSA and everolimus for a while, next in a clinical trial of surufatinib, then back on a double dose of octreotide, and had been embolized several times in the liver. However, he is now 79 years old and no longer wants to receive these particular treatments. He initiated 40 mg cabozantinib dosing based on these discussions. Initial therapy with cabozantinib has been well tolerated.

Disclosures

Dr Paulson has been a consultant/advisor for Agenus, AmMax Bio, AstraZeneca, Bristol Myers Squibb, Exelixis, Ipsen, Jazz Pharmaceuticals, Johnson & Johnson/Janssen, Lilly Pharmaceuticals, Mirati, Novartis, Pfizer, Seagen, and Takeda; has served on the speakers bureau of IDEOlogy Health and MJH Life Sciences; and has received research funding from Buzzard Pharmaceuticals.

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