

Sequencing of Somatostatin-Receptor–Based Therapies in Neuroendocrine Tumor Patients

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Most well-differentiated neuroendocrine tumors (NETs) express high levels of somatostatin receptors, particularly subtypes 2 and 5. Somatostatin analogs (SSAs) bind to somatostatin receptors and are used for palliation of hormonal syndromes and control of tumor growth. The long-acting SSAs octreotide long-acting release and lanreotide are commonly used in the first-line metastatic setting because of their tolerable side effect profile. Radiolabeled SSAs are used both for imaging and for treatment of NETs. ¹⁷⁷Lu-DOTATATE is a β -emitting radiolabeled SSA that has been proven to significantly improve progression-free survival among patients with progressive midgut NETs and is approved for treatment of metastatic gastroenteropancreatic NETs. A key question in management of patients with gastroenteropancreatic and lung NETs is the sequencing of ¹⁷⁷Lu-DOTATATE in relation to other systemic treatments (such as everolimus) or liver-directed therapies. This question is particularly complicated given the heterogeneity of NETs and the near absence of randomized trials comparing active treatment options. This state-of-the-art review examines the evidence supporting use of somatostatin-receptor–targeted treatments within the larger landscape of NET therapy and offers insights regarding optimal patient selection, assessment of benefit versus risk, and treatment sequencing.

Key Words: radionuclide therapy; PRRT; lanreotide; neuroendocrine tumors; octreotide; somatostatin analogs

J Nucl Med 2024; 00:1–9

DOI: 10.2967/jnumed.123.265706

Somatostatin receptor (SSTR) expression is a key feature of well-differentiated neuroendocrine tumors (NETs). Since the 1980s, somatostatin analogs (SSAs) have been used to palliate hormonal syndromes associated with NETs and inhibit tumor growth (1). More recently, radiolabeled SSAs have been developed for diagnostic and therapeutic purposes. ¹¹¹In(In)-pentetreotide scintigraphy (OctreoScan; Curium) was the first widely used SSTR-based scan for staging NETs and characterizing the degree of SSTR expression (2,3). In the past decade, it has been supplanted by SSTR PET imaging, including ⁶⁸Ga(Ga)-DOTATATE and ⁶⁴Cu(Cu)-DOTATATE PET scans, which have substantially higher sensitivity and image resolution (4,5).

β -emitting radiolabeled SSAs, such as ¹⁷⁷Lu(Lu)-DOTATATE or DOTATOC, deliver therapeutic doses of β -radiation (high-energy

electrons) to SSTR-expressing tumors and can result in tumor shrinkage in addition to substantial improvement in progression-free survival (PFS). Newer forms of peptide receptor radionuclide therapy (PRRT) include α -emitting radiolabeled SSAs such as ²¹²Pb(Pb)-DOTAMTATE and ²²⁵Ac(Ac)-DOTATATE (6,7). By emitting much larger particles (2 protons and neutrons) with higher linear energy transfer over an ultrashort particle range, α -emitters can induce double-strand DNA damage and a higher level of cytotoxicity with an improved therapeutic index.

In this state-of-the-art review, we evaluate the role of SSTR-based treatments in patients with advanced NETs of the gastrointestinal tract, pancreas, and lungs. We discuss evidence regarding the efficacy of conventional and radiolabeled SSAs, risks and toxicities, patient selection, and the sequencing of these therapies within the larger therapeutic landscape. Additional topics include early use of PRRT, retreatment with PRRT after progression, and combination approaches.

OVERVIEW OF GASTROENTEROPANCREATIC AND LUNG NETS

NETs can be categorized on the basis of multiple features, including primary site, stage, differentiation, grade, and SSTR expression. Well-differentiated NETs morphologically resemble endocrine cells of origin. Poorly differentiated neuroendocrine carcinomas are highly aggressive malignancies that tend to express SSTRs weakly and are outside the scope of this review. Most well-differentiated NETs are low-grade (Ki-67 index, 0%–2%) or intermediate-grade (Ki-67, 3%–20%) but can occasionally be high-grade (Ki-67 > 20%). For lung NETs, the terms *typical carcinoid* versus *atypical carcinoid* persist and correspond roughly to low and intermediate grades, respectively (8).

Metastatic NETs of different primary sites are quite distinct. Midgut (typically ileal or ileocecal) primaries are the most common and tend to be slow-growing. They are characterized by a high propensity to metastasize to mesenteric lymph nodes (often with desmoplastic features), liver, and, less commonly, peritoneum, ovaries, and bone (9). Metastatic midgut NETs often secrete serotonin, among other vasoactive substances, resulting in diarrhea, flushing, and damage to right heart valves, a condition known as carcinoid syndrome. Metastatic pancreatic NETs also tend to metastasize to the liver and are generally more aggressive than midgut NETs (10). Approximately 10%–20% are associated with hormonal syndromes such as Zollinger–Ellison syndrome (gastrinoma) or Verner–Morrisson syndrome (vasoactive intestinal peptide tumors). Metastatic rectal NETs are rare, often aggressive, and hormonally nonfunctioning (unassociated with a syndrome). Metastatic lung NETs are variable

Received Aug. 18, 2023; revision accepted Dec. 20, 2023.

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Published online Jan. 18, 2024.

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in behavior: most are nonfunctioning, although some can produce serotonin or adrenocorticotrophic hormone.

SSTR expression also varies by primary site. Midgut NETs almost universally express SSTRs, particularly SSTR subtypes 2 and 5, which are targeted by SSAs. Expression is a bit more heterogeneous in pancreatic NETs, particularly higher-grade tumors, and quite heterogeneous in lung NETs, especially atypical ones that can often be SSTR-negative (11).

SOMATOSTATIN ANALOG THERAPY

The SSAs octreotide and lanreotide are often prescribed as a first-line systemic treatment for metastatic NETs. They are considered ideal first-line therapies because of their favorable side effect profile and efficacy, particularly in patients with hormone-related symptoms such as carcinoid syndrome. In a landmark phase II study of short-acting octreotide in patients with carcinoid syndrome, diarrhea and flushing were palliated in 88% of patients, and 5-hydroxyindoleacetic acid was reduced by more than 50% in 72% of patients (12). Subsequent small studies demonstrated equivalent palliation in rarer hormonal syndromes associated with gastrinomas, vasoactive intestinal peptide tumors, and glucagonomas. An exception was insulinomas, in which the effect of SSAs was inconsistent, sometimes leading to improvement and other times exacerbating hypoglycemia because of suppression of the counterregulatory hormone glucagon (13).

After the approval of octreotide for syndrome control, several single-arm studies suggested that SSA therapy may inhibit tumor growth despite the absence of objective radiographic responses. These preliminary observations led to 2 randomized phase III studies designed to test the so-called antiproliferative effect of SSAs. The first of these studies was the PROMID trial, in which 85 patients with metastatic midgut NETs were randomized to 30 mg of long-acting-release octreotide every 4 wk versus placebo, with a primary endpoint of time to progression (14). The study was strongly positive, with an improvement of median time to progression from

6 mo on placebo to 14.5 mo with octreotide (hazard ratio [HR], 0.34; $P < 0.001$).

Subsequently, the CLARINET trial randomized 204 patients with nonfunctioning enteropancreatic NETs to receive 120 mg of lanreotide versus placebo with a primary endpoint of PFS (15). Eligibility requirements included a tumor Ki-67 of less than 10% and SSTR expression on imaging. This trial also met its primary endpoint, with significant improvement in PFS (18 mo on placebo, not reached with lanreotide at the time of primary analysis; HR, 0.47; $P < 0.001$). The HR for progression in the midgut NET population of the CLARINET trial was nearly identical to the HR on the PROMID trial, suggesting that the 2 drugs are likely quite similar in efficacy.

There was no trend for overall survival (OS) benefit in either the PROMID or the CLARINET study (16,17). However, it is essential to note that patients crossed over from the placebo arm to SSA on progression, and neither study was sufficiently powered to evaluate for OS.

Side effects of both drugs tend to be minor. Abdominal cramping and nausea tend to occur more often early in treatment. Steatorrhea is a common side effect that can be palliated with pancreatic enzymes. Gallstone formation is also common but rarely of clinical significance.

As a result of the proven inhibitory effect of SSAs and their benign toxicity profile, either octreotide or lanreotide is typically recommended as first-line treatment for metastatic NETs, both for inhibition of tumor growth and for palliation of hormonal syndromes in patients with functioning tumors. There is little evidence that SSAs inhibit tumor growth in patients with SSTR-negative tumors, although they can still be used to palliate hormonal syndromes. There is also limited evidence to support their use in patients with relatively aggressive tumors (e.g., Ki-67 > 10%) (18). However, it is not unreasonable to try SSAs alone in patients who lack significant symptoms related to tumor burden. It is also important to note that high-level evidence for tumor control exists only for gastroenteropancreatic NETs since neither the PROMID nor the CLARINET trial enrolled patients with lung NETs. In addition, a randomized trial of lanreotide versus placebo in lung NETs (SPINET trial) closed prematurely for poor accrual (19). Nevertheless, it is reasonable to consider SSA therapy in lung NETs, especially if all tumors express SSTR. In tumors with significant symptoms related to tumor burden, or in patients with higher-grade or more aggressive biology, other therapies described below should also be considered in the first-line setting.

PRRT

Since the 1990s, labeling SSAs with radioactive isotopes has been devised to deliver targeted radiation to SSTR-expressing NETs. Radiolabeled SSAs belong to a broader category of treatment known as PRRT. The first generation of PRRT used high doses of ^{111}In -pentetretotide (3). The Auger electrons emitted by this isotope were weakly cytotoxic and rarely led to radiographic responses. The high-energy β -emitting isotopes ^{90}Y and ^{177}Lu were next to be tested, using DOTA as the linker and either octreotide (DOTATOC) or octreotate (DOTATATE) as the peptide in most studies (20–22). Octreotate has an exceptionally high affinity to SSTR subtype 2, strongly expressed in NETs. Early studies using ^{90}Y -peptides reported high rates of severe, grade 3 or 4, nephrotoxicity related to the high tissue penetration and energy of the β -particles (maximum range, 11 mm; maximum energy, 2.27 MeV), despite renal

NOTEWORTHY

- SSAs (octreotide and lanreotide) are often the first-line treatment for patients with metastatic well-differentiated, somatostatin-receptor-positive NETs.
- PRRT with ^{177}Lu -DOTATATE is used in patients with progressive, somatostatin-receptor-positive metastatic disease; however, optimal sequencing of treatments vis-à-vis other systemic and liver-directed therapies, in the absence of dedicated randomized trials, depends on many factors such as primary site, grade, symptom burden, and distribution of metastatic disease.
- Not all patients with metastatic NETs are appropriate candidates for PRRT: particular attention is needed in patients with high-grade or lung NETs (in which SSTR expression is often heterogeneous) and patients with high-burden peritoneal disease (which may increase risk of bowel obstruction)
- Emerging studies (e.g., the COMPETE and COMPOSE trials) will help determine how to best sequence PRRT compared with other standards of care.
- The future of PRRT may include combinations of systemic therapy with PRRT, α -emitting particles, and SSTR antagonists.

protection with positively charged prophylactic amino acid infusions consisting of arginine and lysine (20,22). ^{177}Lu was less nephrotoxic because of its shorter particle range and lower β -energy (maximum range, 2 mm; maximum energy, 0.5 MeV).

Both ^{90}Y - and ^{177}Lu -based radiolabeled SSAs resulted in radiographic responses and relatively long median durations of PFS. Several large institutional databases reported on outcomes in hundreds of treated patients (23–25). One prospectively defined cohort study from Erasmus Hospital in The Netherlands described outcomes in 443 patients with NETs originating in the pancreas, gastrointestinal tract, lung, and unknown primary. Treatment consisted of a fixed administered activity of ^{177}Lu -DOTATATE, 7.4 GBq (200 mCi), administered every 8 wk for 4 treatments with prophylactic arginine/lysine. An objective response rate of 39% was reported for the entire cohort, with a median PFS of 29 mo and a median OS of 63 mo. It is important, however, to note that these outcomes were analyzed only among patients who had received at least 3 cycles of therapy (23).

A prospective phase I/II study conducted at the Institute of European Oncology in Milan enrolled 51 NET patients with escalating administered activities of ^{177}Lu -DOTATATE (26). Among 46 patients assessable for response, an objective response rate of 33% was reported with a median time to progression of 36 mo.

The NETTER-1 trial was the first prospective randomized phase III study of a radiolabeled SSA (27). In this trial, 231 patients with metastatic low- and intermediate-grade, SSTR-positive midgut NETs progressing on standard-dose octreotide were randomized to receive 4 cycles of ^{177}Lu -DOTATATE plus standard-dose octreotide or high-dose octreotide (60 mg). The primary endpoint was PFS. The study met its primary endpoint with a clinically and statistically significant improvement in PFS on the ^{177}Lu -DOTATATE arm (HR, 0.21; $P < 0.0001$). An objective response rate of 18% was observed on the ^{177}Lu -DOTATATE arm versus 3% in the control group. On final analysis, the median investigator-assessed PFS was 25 mo with ^{177}Lu -DOTATATE versus 8.5 mo with high-dose octreotide (28). A nonsignificant 12-mo improvement in OS was reported (48 mo vs. 36.3 mo), likely attenuated by crossover to PRRT in over a third of patients from the control arm (29).

Although the NETTER-1 trial enrolled patients with midgut NETs only, ^{177}Lu -DOTATATE was approved for all gastroenteropancreatic NETs by the Food and Drug Administration and the European Medicines Agency on the basis of both the NETTER-1 trial and the Rotterdam database study. Since the trial was conducted only in patients progressing on SSAs, the current recommendations are to use ^{177}Lu -DOTATATE after progression and not in the first-line setting.

SIDE EFFECTS OF PRRT

Cytopenias are a common side effect of PRRT. Although lymphopenia is the most frequent toxicity, it is rarely of clinical significance, and opportunistic infections are seldom observed, as B lymphocytes are the main subpopulation involved (30). On the NETTER-1 trial, grade 3 or 4 anemia, neutropenia, and thrombocytopenia occurred in 0%, 1%, and 2% of ^{177}Lu -DOTATATE-treated patients. In the Rotterdam study, grade 3/4 anemia, thrombocytopenia, and leukopenia occurred in 5%, 4%, and 5% of patients, respectively (23).

Myelodysplastic syndrome and acute leukemia are among the most serious potential complications of PRRT. The combined incidence of myelodysplastic syndrome and acute myeloid leukemia is

approximately 2%–3%, and the prognosis is poor among patients who experience treatment-related myelodysplasia (23,24). In addition, some evidence indicates that concurrent or sequential administration of cytotoxic chemotherapy may increase the risk of myelodysplastic syndrome or acute leukemia (31–33). Current research focuses on early detection or screening for chronic myelotoxicity evaluating the role of clonal hematopoiesis analysis.

Renal toxicity is a known consequence of ^{90}Y -based PRRT but appears negligible among patients receiving ^{177}Lu -DOTATATE with coadministration of amino acids, if they have an acceptable renal function (e.g., estimated glomerular filtration rate $> 30\text{ mL/min}$) (23,24,29,34). The NETTER-1 study allowed for a controlled assessment of renal function over time. Study patients randomized to ^{177}Lu -DOTATATE demonstrated no evidence of a long-term decline in renal function compared with high-dose octreotide (29).

The risk of bowel obstruction appears to be increased in patients with peritoneal or mesenteric carcinomatosis receiving PRRT (35). In some instances, radiation peritonitis can lead to a frozen abdomen with an irreversible intestinal blockage. There is some evidence that prophylactic corticosteroids may diminish radiation-induced tumor inflammation and complications arising from such inflammatory changes. However, some experts caution against administering steroids before treatment because steroids can reduce SSTR expression.

PRRT AND QUALITY OF LIFE

Large cohort studies have demonstrated that treatment with ^{177}Lu -DOTATATE can improve health-related quality of life and global health status in patients with gastroenteropancreatic and lung NETs (36). A small retrospective study of patients with midgut NETs and carcinoid syndrome treated with ^{177}Lu -DOTATATE demonstrated statistically significant reductions in flushing and diarrhea compared with baseline (37). On the NETTER-1 trial, analysis of health-related quality of life using European Organization for Research and Treatment of Cancer questionnaires demonstrated a statistically significant delay in the decline of quality of life in key metrics including global health, physical functioning, pain, and diarrhea on the ^{177}Lu -DOTATATE arm compared with control. Differences in flushing were not statistically significant between the 2 arms of the study (38). However, another analysis of symptom diaries on NETTER-1 indicated that ^{177}Lu -DOTATATE was associated with a decline in the number of days per month with flushing, diarrhea, and abdominal pain, compared with high-dose octreotide (39).

PRRT IN LUNG NETS

Lung NETs appear to express SSTR relatively heterogeneously; consequently, the number of patients eligible for PRRT is low compared with small-bowel or pancreatic NETs (11,40–42). However, when patients are appropriately selected, outcomes can be comparable to the results of treatment in gastroenteropancreatic NETs (43). ^{177}Lu -DOTATATE is not approved by regulatory authorities for advanced lung NETs but is recommended by guidelines (44).

PRRT IN HIGH-GRADE NETS

Research on PRRT in high-grade NETs is relatively limited. The NETTER-1 study was restricted to patients with grade 1 and 2 tumors (Ki-67 $< 20\%$). However, some retrospective studies have indicated benefits among patients with a Ki-67 of up to 30%–40% (45). Beyond that, median PFS durations tend to be short.

Therefore, when treating patients with high-grade NETs, ensuring that all tumors express SSTR strongly is crucial. Although not mandatory, obtaining dual ¹⁸F-FDG and DOTATATE PET scans can help ensure that all hypermetabolic tumors also express SSTRs and is in fact considered standard practice in many institutions to determine whether a more aggressive component of disease exists that should be treated with an alternate therapy.

PREDICTIVE MARKERS

PRRT is the archetype of a theranostic treatment, with radiolabeled SSAs used for diagnosis and therapy. Not surprisingly, data indicate that the degree of SSTR expression correlates with objective radiologic response. The Krenning scale is used to quantify the degree of radiotracer uptake on ¹¹¹In(In)-pentetreotide scintigraphy: grade 1 indicates tumoral uptake below the normal liver, grade 2 indicates uptake equivalent to the liver, grade 3 indicates uptake above the liver, and grade 4 indicates avidity above splenic uptake (46). A minimum Krenning grade 2 uptake on measurable lesions is considered a threshold for PRRT, and higher degrees of uptake correlate with response. DOTATATE PET scans are more sensitive, and SUVs greater than normal liver are considered a minimum

requirement for treatment. Some studies suggest that SUVs double that of the normal liver are predictive of response (47). A blood RNA-based biomarker in development, the PRRT predictive quotient, integrates a gene expression score with Ki-67 to predict, at baseline, the clinical benefit (disease stabilization or response vs. progression) with ¹⁷⁷Lu-DOTATATE treatment (48). The PRRT predictive quotient was studied in prospective clinical trials in Europe and the United States and demonstrated 96% accuracy in predicting PRRT response (49).

SEQUENCING SSTR-BASED THERAPIES

A key question in managing patients with metastatic NETs is how to best sequence therapies. This issue is complicated because NETs are extremely heterogeneous cancers for which a uniform algorithmic approach is particularly unsuitable. Moreover, until recently, there have been virtually no prospective randomized studies comparing active therapies. Existing trials evaluate primarily PFS and are highly underpowered to assess differences in OS. Thus, recommendations on treatment sequencing are derived from low-level evidence. Table 1 provides a summary of key randomized clinical trials.

TABLE 1
Randomized NET Clinical Trials

Trial	NET type	Patients treated (n)	PFS (mo)	OS (mo)	Objective response rate
PROMID	Midgut NETs	85 (42 octreotide; 43 placebo)	14.3 (octreotide) vs. 6 (placebo) (HR, 0.34; <i>P</i> < 0.0005)	Not reported; (HR, 0.81, <i>P</i> = 0.77)	2% in both arms
CLARINET	Grade 1 and 2 GEP NETs + unknown primary	204 (101 lanreotide; 103 placebo)	Not reached (lanreotide) vs. 18 (placebo) (HR, 0.47; <i>P</i> < 0.001)	Not reported	Not reported
ECOG 2211	Grade 1 and 2 pancreatic NETs	133 (65 TEM; 68 CAPTEM)	14.4 (TEM) vs. 22.7 (CAPTEM) (HR, 0.58; <i>P</i> = 0.022)	53.8 (TEM) vs. 58.7 (CAPTEM) (HR, 0.82; <i>P</i> = 0.42)	33.7% TEM; 39.7% CAPTEM
Sunitinib	Pancreatic NETs	171 (86 sunitinib; 85 placebo)	12.6 (sunitinib) vs. 5.8 (placebo) (HR, 0.32; <i>P</i> < 0.0005)	38.6 (sunitinib) vs. 29.1 (placebo) (HR, 0.73; <i>P</i> = 0.094)	9.3% sunitinib; 0% placebo
OCLURANDOM	Pancreatic NETs	84 (41 PRRT; 43 sunitinib)	20.7 (PRRT) vs. 11 (sunitinib)	Not reported	Not reported
NETTER-1	Grade 1 and 2 midgut NETs	223 (111 PRRT; 112 high-dose octreotide)	28.4 (PRRT) vs. 8.5 (high-dose octreotide)	48 (PRRT) vs. 36.3 (high-dose octreotide) (HR, 0.84; <i>P</i> = 0.30)	18% PRRT; 3% high-dose octreotide
RADIANT-2*	Carcinoid syndrome NETs	429 (200 everolimus; 203 placebo + octreotide)	16.4 (everolimus) vs. 11.3 (control) (HR, 0.77; <i>P</i> = 0.026)	Not reported	2.5% everolimus; 1.9% control
RADIANT-3	Grade 1 and 2 pancreatic NETs	410 (207 everolimus; 203 placebo)	11 (everolimus) vs. 4.6 (placebo) (HR, 0.35; <i>P</i> < 0.001)	Not reported	5% everolimus; 2% placebo
RADIANT-4	Grade 1 and 2 gastrointestinal and lung NETs (nonfunctional)	302 (205 everolimus; 97 placebo + best supportive care)	11.0 (everolimus) vs. 3.9 (control) (HR, 0.48; <i>P</i> < 0.0005)	Not reported	2% everolimus; 1% control

*RADIANT-2 PFS statistical significance was set to 0.0246 and was 0.026.

GEP = gastroenteropancreatic; TEM = temozolomide; CAPTEM = capecitabine and temozolomide.

As noted, we recommend that patients with newly diagnosed metastatic grade 1 or 2 SSTR-positive gastroenteropancreatic NETs be treated with an SSA in the first line. The basis for this is that both octreotide and lanreotide have a proven inhibitory effect on tumor progression and carry a low risk of significant toxicity. A minority of patients may be eligible for cytoreductive surgery. Patients with low symptom and tumor burden and who lack a hormonal syndrome may be eligible for watchful waiting rather than active treatment. In such cases, SSAs can be started after progression. As indicated above, there have been no completed randomized trials of SSAs for patients with metastatic lung NETs; however, evidence suggests that SSAs can be used to treat SSTR-positive tumors, particularly in patients with relatively unaggressive disease.

Evidence for SSA monotherapy in patients with relatively aggressive tumors (e.g., Ki-67 > 10%) is limited. However, octreotide or lanreotide can be considered if the tumor or symptom burden is relatively low. The NETTER-2 study evaluates first-line ¹⁷⁷Lu-DOTATATE versus high-dose octreotide in tumors with a Ki-67 of 10%–55% (NCT03972488).

Beyond first-line treatment, options depend on the primary site. Small-bowel (midgut) NETs are relatively resistant to most systemic therapies (50). Most tyrosine kinase inhibitors and cytotoxic drugs have demonstrated lower response rates in midgut NETs than in pancreatic NETs (51). A randomized phase III study of everolimus plus octreotide versus placebo plus octreotide in patients with a history of carcinoid syndrome (RADIANT 2) did not meet its primary endpoint of improvement in PFS (52). Given the fact that most cases of carcinoid syndrome originate in midgut NETs, everolimus appears to be relatively ineffective in this population.

On the other hand, liver-directed therapies, such as hepatic transarterial embolization, appear to be quite effective in midgut NETs, although evidence derives primarily from small retrospective studies (53–56). Since the liver is the dominant site of metastatic disease, liver-directed therapies represent the main second-line alternative to PRRT in patients with metastatic midgut NETs. There is currently no high-level evidence favoring a particular method of transarterial embolization, with data suggesting similar responses to bland embolization, chemoembolization, or radioembolization. There are also no randomized studies comparing any mode of embolization with PRRT. Thus, decisions on sequencing embolic therapy versus ¹⁷⁷Lu-DOTATATE are individualized, depending on the degree of hepatic versus extrahepatic tumor burden, disease progression sites, SSTR expression, and patient preference (Fig. 1).

Patients with pancreatic NETs have the largest number of approved or guideline-recommended therapies. Beyond first-line SSAs, systemic options include everolimus, sunitinib,

temozolomide, or streptozocin-based chemotherapy regimens, and ¹⁷⁷Lu-DOTATATE. Approval of everolimus was based on the RADIANT 3 study, in which patients with progressive metastatic pancreatic NETs were randomized to everolimus versus placebo (57). Despite response rates of less than 10%, the study showed statistically significant improvement in PFS (median, 11.0 vs. 4.6 mo; HR, 0.35; *P* < 0.001). Toxicities include oral aphthous ulcers, pneumonitis, hyperglycemia, fatigue, and immunosuppression. Approval of sunitinib was based on a phase III trial in which patients with progressive metastatic pancreatic NETs were randomized to sunitinib versus placebo (58). The outcomes were remarkably similar to RADIANT 3, with statistically significant improvement in PFS (median, 11.4 vs. 5.5 mo; HR, 0.42; *P* < 0.001) and an objective response rate of 9% with sunitinib. Side effects of sunitinib include fatigue, hypertension, diarrhea, palmar-plantar erythrodysesthesia, and increased risk of cardiovascular events.

The capecitabine/temozolomide chemotherapy regimen is associated with much higher objective radiographic response rates of approximately 50% (59). In the randomized phase II ECOG2211 trial, capecitabine/temozolomide was compared with single-agent temozolomide in patients with progressive pancreatic NETs (60). Median PFS was 22.7 mo with capecitabine/temozolomide (vs. 14.4 mo with temozolomide; *P* = 0.02), and the confirmed radiographic response rate was 40%. This regimen is relatively well tolerated, with the main toxicities consisting of cytopenias.

The sequencing of therapies beyond first-line SSAs is particularly complicated for patients with SSTR-positive pancreatic NETs. The OCLURANDOM trial was among the first prospective trials to randomize patients to 2 active treatments: ¹⁷⁷Lu-DOTATATE versus sunitinib (61). Although this randomized phase II study of 84 patients was too underpowered to allow for statistical comparison of the 2 arms, the differences in outcomes favoring ¹⁷⁷Lu-DOTATATE were stark: a median PFS of 20.7 mo (90% CI, 17.2–23.7) with ¹⁷⁷Lu-DOTATATE versus 11 mo (8.8–12.4) with sunitinib. This study strongly suggests (although it does not prove) that second-line ¹⁷⁷Lu-DOTATATE is a superior option to sunitinib for progressive pancreatic NETs. The larger phase III COMPETE study, which compares ¹⁷⁷Lu-DOTATOC with everolimus in progressive nonfunctioning gastroenteropancreatic NETs, has completed accrual, but results are still pending.

It is important to note that liver embolization is also an option for patients with liver-dominant pancreatic NETs. Most guidelines do not currently recommend a particular sequence of therapies for patients with metastatic pancreatic NETs (62). However, for patients with extrahepatic disease and strong SSTR expression, ¹⁷⁷Lu-DOTATATE represents an option that likely has the least adverse impact on patient quality of life. Median PFS almost certainly exceeds outcomes with everolimus or sunitinib. The advantage of PRRT compared with capecitabine/temozolomide chemotherapy is less certain. For patients with high tumor and symptom burden who require rapid cytoreduction, chemotherapy with capecitabine/temozolomide (or other cytotoxic regimens) may be preferred because of the rapid responses and the ability to initiate treatment quickly (Fig. 2). The capecitabine/temozolomide regimen is also appropriate for patients with well-differentiated grade 3 pancreatic NETs (63–66).

For metastatic lung NETs, everolimus is the only therapy approved by regulatory authorities on the basis of the phase III RADIANT 4 trial in which patients with nonfunctioning gastrointestinal and lung NETs were randomized to everolimus versus

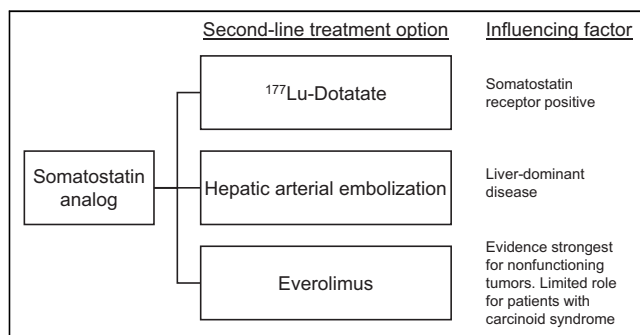


FIGURE 1. Second-line options for patients with metastatic, SSTR-positive, progressive midgut NET after SSA.

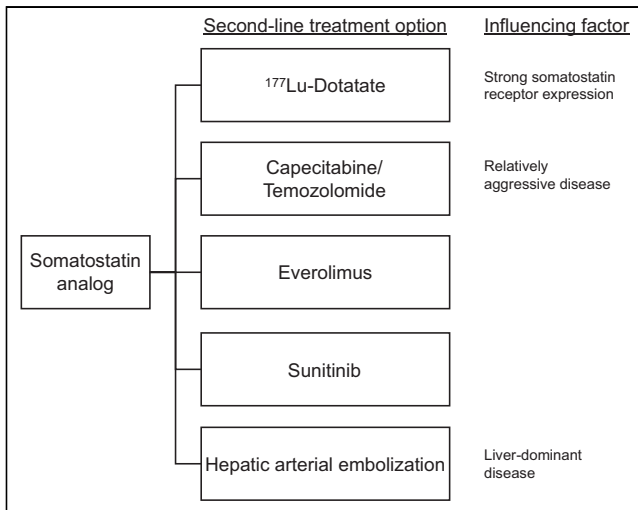


FIGURE 2. Second-line options for patients with metastatic, SSTR-positive, progressive pancreatic NET after SSA.

placebo (67). The study, which included a plurality of lung NETs, demonstrated an improvement in median PFS from 3.9 mo on placebo to 11.0 mo with everolimus (HR, 0.48; $P < 0.001$). Non-randomized studies suggest that median PFS is likely higher with ¹⁷⁷Lu-DOTATATE in patients with SSTR-positive lung NETs (43). However, ¹⁷⁷Lu-DOTATATE is not approved by regulatory authorities for lung NETs. Some guidelines recommend ¹⁷⁷Lu-DOTATATE only after progression or intolerance of everolimus based on a higher level of evidence supporting the latter drug. A randomized phase II study comparing ¹⁷⁷Lu-DOTATATE with everolimus in metastatic lung NETs is open (NCT04665739).

For patients with other uncommon primary sites (e.g., rectum, stomach, or duodenum), the main alternative to PRRT is everolimus, also based on the RADIANT 4 study. The COMPETE study will help determine the optimal sequence of systemic therapies in patients with these tumor types (NCT03049189). As with other primary sites, liver embolization represents an option for patients with unresectable, liver-dominant disease (Fig. 3).

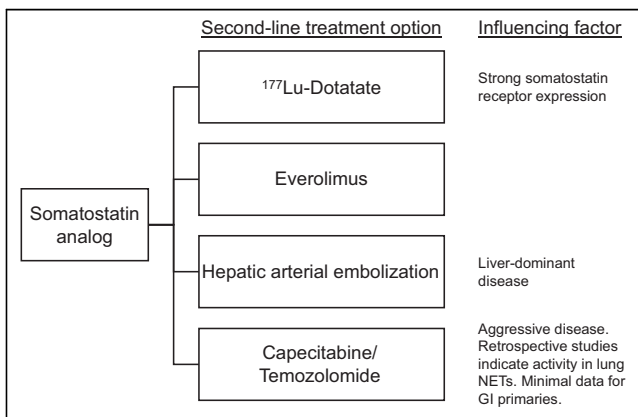


FIGURE 3. Second-line options for patients with metastatic, SSTR-positive, progressive nonmidgut gastrointestinal or lung NET after SSA. GI = gastrointestinal.

SSAS BEYOND PROGRESSION

In patients with hormonally functional tumors, the SSA octreotide or lanreotide is typically continued indefinitely beyond progression through multiple lines of treatment to control hormonal syndromes. Even patients with suboptimal control of symptoms such as flushing or diarrhea may derive some benefit from these drugs compared with discontinuation.

A more controversial question is whether to continue SSAs beyond progression in patients with nonfunctional tumors. This question is particularly salient among patients receiving PRRT. On the NETTER-1 trial, which enrolled patients with functional and nonfunctional tumors, all patients in the ¹⁷⁷Lu-DOTATATE arm continued standard-dose octreotide despite having progressed on this drug before enrollment. Retrospective studies have yielded data supporting this practice: one study showed markedly prolonged PFS and OS in patients who continued SSA during or after PRRT compared with those who stopped (68). However, confounding variables probably substantially impact nonrandomized studies such as these. For example, patients who progress rapidly on SSAs are more likely to discontinue the drug than patients with mild progression. A small, randomized trial comparing maintenance octreotide versus observation after PRRT showed no PFS benefit from maintenance SSA (69). Therefore, we can say that there is currently no compelling evidence to support maintenance SSA after progression in patients with nonfunctioning tumors.

CONTINUING SSA IN FUNCTIONING TUMORS WHILE ON PRRT

Patients with carcinoid syndrome or other hormonal symptoms typically continue octreotide or lanreotide while receiving PRRT. In many studies, including NETTER-1, long-acting SSAs were stopped more than 6 wk before each PRRT cycle, and short-acting octreotide was stopped more than 24 h before treatment. The rationale for this practice was the concern that cold SSAs would compete with radiolabeled SSAs for SSTR binding. However, numerous recent studies have called this practice into question by demonstrating that the impact of SSAs on SSTR imaging is minimal and that SSAs can preferentially decrease the SSTR expression of normal organs compared with NETs. Food and Drug Administration guidance recommends suspending long-acting SSA for 4 wk or more before PRRT treatment. Therefore, one potential option is to administer a long-acting SSA after each treatment and then 4 wk later, precisely at the midpoint between the 8-wk cycle of ¹⁷⁷Lu-DOTATATE. However, it is debatable whether there is a need for any precise synchronization of SSAs and PRRT.

FIRST-LINE PRRT

Because of risks associated with PRRT, including myelodysplastic syndrome or acute leukemia, using ¹⁷⁷Lu-DOTATATE as first-line therapy is generally not recommended. Exceptions may include patients with a high tumor burden in whom early aggressive treatment is necessary. The NETTER 2 trial is investigating ¹⁷⁷Lu-DOTATATE versus high-dose octreotide in patients with gastroenteropancreatic NETs and high-intermediate-grade or high-grade disease (Ki-67, 10%–55%) (NCT03972488). The COMPOSE study is also evaluating the early use of PRRT with ¹⁷⁷Lu-DOTATOC in patients with relatively high-grade tumors (NCT04919226). The primary endpoint of both trials is PFS. However, it will be challenging to ascertain whether the earlier use of PRRT impacts the ultimate endpoint of OS.

There are also small retrospective series describing the neoadjuvant use of PRRT, particularly in patients with borderline-resectable pancreatic NETs or patients with oligometastases in whom some tumor shrinkage is necessary to enable surgery with negative margins (70). However, no evidence supports postoperative adjuvant PRRT to eradicate micrometastases. Indeed, the relatively long particle range of β -emitters such as ^{177}Lu -DOTATATE may be poorly suited for targeting submillimeter tumors.

AGGRESSIVE TRANSFORMATION OF NETS

The transformation of metastatic NETs from relatively slow-growing to highly aggressive is a phenomenon that has been documented, particularly for pancreatic NETs. It is possible (but not certain) that cytotoxic drugs such as chemotherapy or PRRT increase the risk of this occurrence by inducing somatic intratumoral mutations or by selectively killing the more differentiated population. Indeed, one case series documented the transformation of well-differentiated NETs to poorly differentiated neuroendocrine carcinomas in 7 of 152 patients (5%) who had received PRRT (71). All 7 had pancreatic NETs (among 39 patients with pancreatic NETs) and had also received prior temozolomide chemotherapy. It is unclear whether this phenomenon should influence treatment sequencing for patients with pancreatic NETs.

Once transformation develops, prognosis is poor, and treatments used in low-intermediate-grade tumors are of doubtful efficacy, even if SSTR expression is retained. For very aggressive disease, platinum-based regimens such as carboplatin/etoposide or 5-fluorouracil/oxaliplatin are often recommended (72).

RETREATMENT, COMBINATION THERAPY, AND NOVEL PRRT AGENTS

Retreatment with PRRT beyond the standard 4 doses is recommended for patients who experience benefit from initial treatment, ideally those who have at least 12 mo of disease control after therapy (73–76). The lifetime maximum of standard-dose PRRT is typically 6–8 cycles. This practice is currently based on retrospective data; there is currently a trial exploring this in a randomized fashion (retreatment with ^{177}Lu -DOTATATE vs. everolimus; NCT05773274).

There have been several studies exploring the combination of PRRT with various cytotoxic and targeted therapies. The combination of capecitabine/temozolomide and PRRT with either ^{177}Lu -DOTATATE or ^{90}Y -DOTATOC has been explored in several small studies, either sequentially or in a sandwich fashion, and although response rates tend to be higher than for monotherapy, there have not been significant improvements in PFS or OS compared with PRRT alone (31,33,77). Other avenues are exploring combinations of PRRT with radiosensitizing drugs (78–80).

In addition to combination therapies, novel PRRT agents— α -emitters and SSTR antagonists—are being explored in several trials (6,7,81). α -emitters allow for a more targeted therapy because of their shorter penetration range and higher linear energy, and SSTR antagonists can occupy more binding sites with a lower dissociation rate than SSTR analogs, leading to higher tumor uptake and lower risk of damage to surrounding healthy tissue. There are several ongoing clinical trials, phase II and phase III, exploring α -PRRT with ^{212}Pb -DOTAMTATE and ^{225}Ac -DOTATATE in the PRRT-naïve and -refractory settings. A clinical trial with the SSTR antagonist ^{177}Lu -satoreotide tetraxetan recently reported a response rate of 21% and median PFS of 28 mo, warranting further evaluation of the drug in future studies (82).

CONCLUSION

The SSAs octreotide and lanreotide represent a standard first-line therapy for patients with metastatic, unresectable well-differentiated gastroenteropancreatic NETs, both for control of tumor growth and for inhibition of hormonal syndrome. They are also probably effective in patients with SSTR-positive lung NETs, although high-level evidence is lacking. The radiolabeled SSA ^{177}Lu -DOTATATE is an appropriate therapy for patients with SSTR-positive disease progression in the second-line setting or beyond. Evidence from a phase III trial exists only for midgut NETs (NETTER-1). More recently, a randomized phase II study (OCLURANDOM) demonstrated substantially improved PFS with ^{177}Lu -DOTATATE versus sunitinib, although the small sample size precluded definitive conclusions. When PRRT is initiated, SSAs should be continued in most patients with carcinoid syndrome or other hormonal syndromes. Evidence for continuation of SSAs beyond progression in nonfunctioning NETs is weak.

As of now, no phase III trials have been completed comparing PRRT with other standard, approved systemic or liver-directed therapies. Decisions on treatment sequencing should be individualized on the basis of disease and patient factors. Multidisciplinary tumor boards at centers of expertise, incorporating perspectives from relevant medical specialties (e.g., medical oncology, interventional radiology, surgery, and nuclear medicine), can help to optimize treatment strategies.

The future of PRRT in NETs will likely include α -emitting isotopes that have the potential to improve the therapeutic index of radiolabeled SSAs. Prospective clinical trials will help determine whether these agents will replace the β -emitter ^{177}Lu -DOTATATE or whether they will be used primarily for patients who are refractory to standard PRRT.

DISCLOSURE

Jonathan Strosberg is a consultant or on the speaker bureau for Novartis and Ipsen and receives institutional research funding from RayzeBio and Alphamedix. Ghassan El-Haddad is a consultant for Bayer, Boston Scientific Corp., Novartis, Terumo, and NorthStar. Diane Reidy Lagunes is a consultant for Novartis and receives institutional research funding from Novartis, Ipsen, and Merck. Lisa Bodei is a consultant (uncompensated) for Novartis, Ipsen, ITM, Point Biopharma, RayzeBio, Precirix, and Great Point Partners and receives institutional research funding from Novartis. No other potential conflict of interest relevant to this article was reported.

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