Journal of Nuclear Medicine, published on February 8, 2019 as doi:10.2967/jnumed.118.214882

Medical Management of Gastroenteropancreatic Neuroendocrine Tumors: Current Strategies and Future Advances

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Keywords: Management; Gastroenteropancreatic Neuroendocrine tumors; Carcinoid tumors; Systemic treatment

Running title: Medical Treatment of GEP-NETs

Noteworthy points:

- **GEP-NETs can be classified according to stage, grade, differentiation, primary site, tumor burden, and somatostatin receptor expression**
- **Somatostatin analogs are typically first-line treatment of choice for patients with well-differentiated, somatostatin-receptor expressing tumors**
- **^{177}Lu-dotatate is an appropriate treatment for patients with progressive, metastatic, somatostatin-receptor positive GEP-NETs; however choice of treatment needs to be considered within the wider therapeutic landscape.**

ABSTRACT

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are relatively rare neoplasms, characterized by a propensity to secrete hormones which cause distinct clinical syndromes. During the past decade, the systemic treatment landscape has improved significantly: new options include everolimus, an inhibitor of the mammalian target of rapamycin (mTOR), sunitinib, an angiogenesis inhibitor, and cytotoxic regimens such as capecitabine and temozolomide. Moreover, the recent approval of the radiolabeled somatostatin analog ^{177}Lutetium(Lu)-dotatate has had a significant impact on management of neuroendocrine malignancies. In this review, we discuss advances in the medical management of GEP-NETs within the context of the larger multidisciplinary approach to these diseases.

INTRODUCTION

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are heterogeneous neoplasms derived from neuroendocrine cells. GEP-NETs are considered rare, although annual incidence has increased significantly in the past several decades, now exceeding 5 in 100,000 in the United States.[1] Due to relatively long median survival durations, the prevalence of GEP-NETs in the population surpasses that of most other gastrointestinal cancers, including gastric or pancreatic adenocarcinoma. GEP-NETs can arise from hereditary syndromes such as multiple endocrine neoplasia type 1, neurofibromatosis type 1 and Von Hippel-Lindau's disease; however, the large majority are sporadic.[2] They are highly diverse neoplasms that can be categorized using multiple criteria, one of which is embryonic derivation: foregut tumors originate from the stomach, duodenum, and pancreas, midgut tumors from the jejunum, ileum and proximal colon, and hindgut tumors from the distal colon and rectum. As a general rule, midgut tumors are highly prone to metastasize, but generally slow growing.[3] Midgut NETs are also characterized by a tendency to produce serotonin as well as other hormones, resulting in the carcinoid syndrome.

One of the most important classifications of GEP-NETs is based on histologic differentiation and grade. Differentiation refers to the extent to which neoplastic cells resemble endocrine cells of origin. Poorly differentiated tumors tend to be highly aggressive malignancies, whereas well-differentiated tumors tend to progress more indolently.[4] Tumor grade refers to the proliferative activity of tumor cells, measured either using mitotic rate or Ki-67 index. Tumors with mitotic rate or ki-67 index >20% are classified as high grade. Loss of differentiation tends to correlate strongly with grade, and virtually all poorly differentiated cancers are high grade with Ki-67 indexes usually above 50%.[5] New World Health Organization (WHO) classifications recognize the existence of tumors that are both well-differentiated and high-grade, originating primarily in the pancreas.[6] As a matter of terminology, the term 'neuroendocrine tumor' is used to refer to a well-differentiated neuroendocrine neoplasm, whereas 'neuroendocrine carcinoma (NECA)' defines a poorly differentiated neoplasm. Well-differentiated, high grade NETs are associated with higher rates of somatostatin receptor expression and substantially improved overall survival durations compared to poorly-differentiated NECAs.[7, 8]

Other ways of classifying GEP-NETs include disease stage, tumor burden, extent of hepatic versus extrahepatic disease, hormone production, and somatostatin receptor expression. The latter category is increasingly important with the emergence of radiolabeled somatostatin analogs (SSAs) which rely on somatostatin receptor (SSTR) expression for their activity.

SOMATOSTATIN ANALOG THERAPY

Somatostatin is a peptide hormone that binds to SSTR subtypes 1-5 and inhibits the secretion of other hormones such as serotonin, gastrin, vasoactive intestinal peptide (VIP), and glucagon.[9-12] Due to its short half-life of several minutes, administration of somatostatin on an outpatient basis is not practical. Long-acting SSAs include octreotide LAR and lanreotide. Both analogs bind primarily to SSTR subtypes 2 and 5.[13, 14] SSAs were initially shown to alleviate hormonal symptoms such as flushing and diarrhea associated with carcinoid syndrome, necrolytic migratory erythema (NME), cachexia and hyperglycemia in glucagonoma syndrome, and severe watery diarrhea associated with VIPoma syndrome. SSAs were subsequently found to inhibit tumor growth despite very rare objective radiographic responses.

The phase III PROMID study was the first randomized trial to evaluate the antiproliferative effects of an SSA.[15] The trial randomized 85 patients with midgut NETs to receive octreotide long-acting repeatable (LAR) 30mg every 4 weeks versus placebo, with time to progression (TTP) as the primary endpoint. The study met its primary endpoint with significant improvement in TTP (14.3 months versus 6 months, HR 0.34; p = 0.000072). More recently, the phase III CLARINET study evaluated lanreotide depot 120 mg every 4 weeks against placebo in hormonally non-functioning, somatostatin receptor positive GEP-NETs with Ki-67 index less than 10%.[16] In this trial, lanreotide was associated with a significantly prolonged progression-free survival (PFS) compared to placebo (median not reached versus 18 months, HR 0.47; p= 0.001). Of note, the hazard ratio for PFS in the midgut population of the CLARINET trial was nearly identical to the hazard ratio for TTP in the PROMID trial.

SSAs are generally well-tolerated and associated with fewer side effects or risks than other anti-neoplastic therapies. Steatorrhea is one of the chief toxicities, and can usually be managed effectively with pancreatic digestive enzymes. Cholelithiasis is a long-term complication caused by inhibition of physiologic gallbladder contraction. Mild hyperglycemia and bradycardia are other side effects, but rarely of clinical significance.

At this time, there is no convincing data to favor use of one SSA versus the other, and guidelines endorse use of either octreotide or lanreotide, both for syndrome and tumor control. There is some evidence to suggest the escalation of dose or frequency of SSA beyond label doses can be used to control refractory carcinoid syndrome: this strategy seems to be particularly useful when symptoms worsen towards the end of each 4-week injection cycle.[17, 18] Patients with suboptimal syndrome control can also use rescue injections of short-acting

octreotide. There is no evidence to support switching from one SSA to another at a time of radiographic progression. Due to their benign side effect profile and evidence of efficacy in multiple clinical trials, SSAs are often the first-line treatment of choice for well-differentiated NETs. Whether evidence of SSTR expression is required as a criterion for use is a question of some controversy.

TELOTRISTAT ETHYL

Telotristat ethyl is an oral inhibitor of tryptophan hydroxylase, the rate-limiting enzyme in serotonin biosynthesis. It was developed to treat refractory diarrhea related to carcinoid syndrome. The phase 3 TELESTAR study assessed the safety and efficacy of 2 doses of telotristat (250 mg and 500 mg, each taken three times daily) combined with SSA versus placebo plus SSA in patients with well-differentiated metastatic NETs who experienced uncontrolled diarrhea (≥4 bowel movements daily) on SSA.[19] There was a statistically significant reduction in in bowel movement frequency using telotristat compared to placebo averaged over a 12-week double blind period [-0.81 bowel movement per day for 250 mg ($p < .001$ versus placebo), and –0.69 for 500 mg ($p < .001$)]. A significant reduction in urine 5-HIAA level was observed with either dose of drug (decreased by mean of 40 mg and 57.7 mg per 24 hours with 250 and 500 mg, respectively). The drug was overall well tolerated and safe. There was a slightly higher incidence of nausea and depression with the 500 mg dose of telotristat as compared with either the lower 250 mg dose or placebo. These results supported the efficacy and safety of telotristat, and a dosage of 250 mg 3 times per day was granted approval by the Food and Drug Administration (FDA) for refractory carcinoid-syndrome-related diarrhea. There is no clear evidence that telotristat impacts flushing, which is not thought to a serotonergic symptom, nor is there evidence that it inhibits tumor growth. It is possible that telotristat can inhibit progression of carcinoid heart disease, but clinical evidence for this is limited.

EVEROLIMUS

The mTOR enzyme is a threonine kinase which is crucial in regulation of cell proliferation and metabolism. It also mediates signaling from growth factor receptors including insulin-like growth factor receptor (IGFR).[20, 21] Previous preclinical studies on pancreatic neuroendocrine cell lines (BON-1) have shown that mTOR inhibitors (rapamycin and everolimus) can decrease NET cell growth.[22, 23] Everolimus is an oral mTOR inhibitor which has been studied extensively in GEP-NETs. Based on favorable single-arm data, several phase III trials were launched to evaluate everolimus in various NET populations. The RADIANT 3 study evaluated everolimus

10mg versus placebo in patients with low- and intermediate-grade pancreatic NETs. [24] The primary endpoint was PFS, and results demonstrated a statistically significant PFS improvement from a median of 4.6 months on the placebo arm to 11 months on the everolimus arm (HR 0.35, p <0.001). The objective response rate (ORR) was only 5% on the everolimus arm (versus 2% in the placebo arm). Although the study was not powered to evaluate overall survival (OS), there was a mild and statistically insignificant trend towards OS benefit with everolimus in this population.

The RADIANT 2 study evaluated everolimus plus octreotide versus placebo plus octreotide in patients with advanced gastrointestinal and lung NETs (non-pancreatic) and with history of carcinoid syndrome.[25] Due to the latter eligibility criterion, the study predominantly enrolled a population of relatively slow-growing midgut NETs. This study fell just short of meeting its endpoint of statistically significant improvement in PFS (HR 0.77, p = 0.026 with pre-specified statistical significance threshold of p < 0.024), and thus did not lead to FDA approval of everolimus in this population of patients. Moreover, subsequent survival analysis showed a nonsignificant, mild trend toward decreased OS with everolimus versus placebo.[26] `

The final RADIANT study, RADIANT 4, evaluated everolimus versus placebo in hormonally non-functional low and intermediate-grade gastrointestinal and lung NETs with radiographic progression over a period of 6 months.[27] Concurrent SSAs were prohibited. This trial enrolled a relatively aggressive population of patients and met its primary endpoint of improvement in PFS (11 months versus 3.9 months, HR 0.48, p <0.00001) with promising interim OS (HR, 0.64; p = .037). Everolimus was FDA approved for gastrointestinal and lung NETs based on results of the RADIANT 4 study.

Based on results of the RADIANT 3 and RADIANT 4 trials, everolimus was demonstrated to have efficacy across a wide spectrum of GEP-NETs and should be especially considered in patients with clinically significant disease progression. However, results of the RADIANT 2 study suggest caution when prescribing the drug to patients with slow-growing midgut NETs and carcinoid syndrome.

The most common side effects of everolimus include oral aphthous ulcers, rash, diarrhea, hyperglycemia, hyperlipidemia, pneumonitis and immunosuppression resulting in atypical infections. However, with dose reductions and appropriate supportive measures, such as

dexamethasone mouth rinse for oral ulcer prevention, most patients can tolerate everolimus for a long treatment period.

ANGIOGENESIS INHIBITORS

GEP-NETs are highly vascular cancers. They frequently express the vascular endothelial growth factor (VEGF) ligand and its receptors, and high levels of circulating VEGF are associated with tumor progression.[28] The tyrosine kinase inhibitor (TKI) sunitinib, which targets VEGF receptors 1, 2, and 3, as well as platelet-derived growth factor receptor (PDGFR), was evaluated in a phase II trial of pancreatic and non-pancreatic (carcinoid) NETs. ORR in the pancreatic NET cohort was 16.7% (versus 2% in carcinoid tumors).[29] These results led to a randomized phase 3 trial of sunitinib in patients with advanced, well-differentiated pancreatic NETs.[30] 171 patients were randomized to receive sunitinib 37.5 mg daily versus placebo. There was significant PFS benefit with sunitinib, and improvement of median PFS from 5.5 months to 11.4 months (HR, 0.42; p <.001) with objective response rate of 9.3%. The study was not powered to show OS improvement, however there was a nonsignificant trend towards improved OS with sunitinib (median OS 38.6 months for sunitinib versus 29.1 for placebo, p = .094). The most documented side effects of sunitinib were diarrhea, nausea, vomiting, palmar-plantar erythrodysesthesia, fatigue and hypertension.

Other antiangiogenic agents for management of GEP-NETs have been investigated in phase II and III trials. The phase III SWOG S0518 trial, evaluated the efficacy of bevacizumab (anti-VEGF-A antibody) and octreotide vs interferon and octreotide in GEP-NETs patients.[31] Despite promising phase II data, there was no significant improvement in PFS with bevacizumab (16.6 months in bevacizumab arm versus 15.4 months with interferon, HR 0.93; p = 0.55). Other antiangiogenic TKIs, including pazopanib, axitinib, and sorafenib have been investigated in several phase II trials.[32, 33] An ongoing prospective randomized phase II trial of pazopanib vs placebo has enrolled patients with progressive non-pancreatic NETs (NCT01280201). In-addition to monotherapy, the combination of VEGF and mTOR inhibition has shown promising results. For example, a randomized study in 150 patients with progressive pancreatic NETs compared everolimus monotherapy to everolimus plus bevacizumab.[34] Although there was remarkable improvement in response rate in the combination arm with 31% ORR, there was only modest PFS benefit (16.7 months vs 14, p =0.12).

At this time, with are no prospective studies comparing everolimus with sunitinib in pancreatic NETs, a population where both drugs are approved for progressive disease. The results of the

RADIANT 3 study and the phase III sunitinib study in pancreatic NETs suggest very similar benefit and tolerability. Biomarkers predicting response to either everolimus or antiangiogenic drugs have not been identified. At this time, patient comorbidities may dictate choice of treatment. For example, sunitinib is relatively contraindicated in patients with uncontrolled hypertension or cardiovascular disease whereas use of everolimus is discouraged in patients with advanced diabetes.

CYTOTOXIC CHEMOTHERAPY IN WELL-DIFFERENTIATED NET

Streptozocin-based chemotherapy regimens have been a standard treatment of pancreatic NETs for several decades.[35] In recent years, the oral alkylating drug temozolomide has been found to be active in a variety of NETs, particularly pancreatic NETs. One retrospective analysis of temozolomide in a heterogenous population of NETs demonstrated an ORR of 14%.[36] A prospective phase II study of temozolomide plus thalidomide demonstrated a response rate of 45% in pancreatic NETs versus 7% in carcinoid tumors.[37] Another phase II study of temozolomide combined with bevacizumab yielded similar results: an ORR of 33% in pancreatic NET versus 0% in carcinoid tumors.[38]

The combination of temozolomide and capecitabine (TC) was shown to be synergistic in cell line studies.[39] Based on promising phase I data, an analysis of TC in 30 consecutively treated pancreatic NETs reported an ORR of 70% and median PFS of 18 months.[40] Based on these results, a cooperative group trial (ECOG 2211) randomized 144 patients with progressive pancreatic NETs to received temozolomide monotherapy (T) versus TC, with PFS as the primary endpoint.[41] The results showed that the TC regimen was associated with significant improvement in PFS (median PFS was 22.7 months for TC vs. 14.4 months for T, HR = 0.58, p = 0.023) and OS (median OS not reached for TC versus 38.0 months for T, HR = 0.41, p = 0.012). Overall, the TC regimen is relatively tolerable, with cytopenias, particularly thrombocytopenia, representing the most clinically significant grade 3 or 4 toxicities. There is significant controversy as to whether expression of O^6-methyl-guanine-methyl-transferase (MGMT) predicts response to temozolomide-based chemotherapy. [42]
Based on results of the ECOG 2211 trial as well as single arm data, TC can be considered a standard of care regimen in pancreatic NETs. The activity of this regimen in non-pancreatic NETs is almost certainly inferior, but has yet to be clearly established. Intravenous streptozocin

based regimens such as streptozocin plus 5-fluorouracil (5-FU), streptozocin plus doxorubicin, or combinations of all three drugs, remain a valid option for pancreatic NETs.[43]

CYTOTOXIC CHEMOTHERAPY IN POORLY DIFFERENTIATED NECA

Poorly-differentiated NECAs are treated similarly to small cell lung cancer, with etoposide plus platinum (either cisplatin or carboplatin) as the standard first-line regimen. This combination has been used to induce response rates of about 45-60% but with short duration of response (8–9 months), median survival rates less than 2 years and significant toxicity.[44, 45] With lack of supportive literature for standard of care, most patients who progress after platinum/etoposide regimen will have limited therapeutic options. There are small trials and case series suggesting that regimens used in GI malignancies (i.e. 5-FU plus oxaliplatin [FOLFOX] or 5-FU combined with oxaliplatin and irinotecan [FOLFIRINOX]) are active as well.[46, 47] Unfortunately, preliminary data from immunotherapy trials suggest that poorly differentiated NECAs are less immunosensitive than small cell lung cancer.[48, 49]

RADIOLABELED SOMATOSTATIN ANALOG THERAPY

Radiolabeled SSA therapy (also known as peptide receptor radionuclide therapy; PRRT), is an emerging form of targeted radiotherapy. Radiolabeled SSAs consist of a radionuclide isotope, a somatostatin analog (peptide), and a chelator which binds them, enabling the delivery of radioactive isotopes to SSTR expressing tumors. Octreotide or the modified octapeptide octreotate are the most widely used SSAs, and DOTA is most commonly used as the chelating molecule. PRRT activity correlates with levels of somatostatin receptor uptake on somatostatin receptor imaging.[50]

Data from early studies of PRRT using octreotide radiolabeled with high doses of Auger-electron emitting Indium-111 (^{111}In) showed evidence of symptom palliation, but low rates of radiographic response.[51, 52] Subsequent single-arm studies showed much higher radiographic response rates using SSAs radiolabeled with the beta emitters Yttrium-90 (^{90}Y) or Lutetium-177 (^{177}Lu) and encouraging durations of median PFS.[53] Long-term toxicity analyses have demonstrated a roughly 2.5% risk of myelodysplastic syndrome (MDS) or acute leukemia (AL).[54, 55] However, these single-arm studies were mostly large institutional series

rather than prospective phase II studies, and often lacked strict eligibility criteria, intention-to-treat data analysis, and independent radiographic review.

The phase III NETTER-1 was the first randomized, prospective trial of a radiolabeled somatostatin analog.[56] 231 patients with SSTR-expressing midgut NETs progressing on standard-dose octreotide were randomized to receive ^{177}Lu-DOTATATE (4 doses of 7.4GBq every 8 weeks) combined with standard-dose octreotide LAR 30 mg, or high-dose octreotide LAR (60 mg). The primary endpoint was PFS. The study met its primary endpoint with 79% reduction in risk of progression or death (median PFS not reached versus 8.4 months, HR 0.21; p <0.00001). Objective response rate was significantly higher in ^{177}Lu-Dotatate group compared to control group (18% vs 3%, *P* <.001). Interim analysis of OS, at the time of PFS analysis, demonstrated preliminary improvement of OS in the PRRT arm (HR 0.4, *P* = 0.004).

Overall, treatment was well tolerated with the most documented side effects consisting of grade 1-2 nausea and vomiting, attributable to commercial amino acids used for renal prophylaxis. There was no excess nephrotoxicity observed in the ^{177}Lu-dotatate arm. Treatment with ^{177}Lu-dotatate treatment was also associated with significant delay in time to deterioration in key quality of life (QoL) domains including global health, physical functioning, role functioning, diarrhea, pain and fatigue.[57] Based on results of the NETTER-1 study, as well as single-arm registry data, ^{177}Lu-dotatate was approved for treatment of advanced GEP-NETs.

LIVER DIRECTED THERAPY

The liver is the dominant site of metastases for GEP-NETs, and liver-directed treatments, including cytoreductive surgery and hepatic arterial embolization, have been used for decades despite limited prospective trial data.

Surgical cytoreductive surgery can be palliative for patients with symptomatic metastases, and is associated with favorable long-term survival outcomes. [58, 59] Traditionally, the ability to resect 90% of tumors has been considered a critical eligibility criterion. Decisions regarding surgical resectability of disease are often made early in the course of treatment. Data supporting surgical cytoreduction are exclusively retrospective, and consequently the level of evidence supporting this approach is inherently limited.

Liver embolization therapy relies on the fact that metastatic tumors in the liver derive their blood supply primarily from the hepatic arterial circulation, whereas normal liver parenchyma is

supplied primarily from the portal venous circulation. Embolization of microparticles without chemotherapy (bland embolization), or admixed with chemotherapy (chemoembolization) have both been described extensively in the NET literature. Evidence supporting liver embolization originates primarily from retrospective institutional series, which demonstrate ORRs of roughly 50% and an even higher rate of symptomatic improvement. Median durations of PFS are generally in the 12-24 month range.[60]

Liver embolization is primarily recommended for patients with progressive, unresectable, bilobar liver metastases. There are no completed randomized prospective trials comparing various embolization modalities; the currently open randomized RETNET study is comparing bland embolization versus chemoembolization and drug eluting bead embolization for treatment of metastatic NETs to the liver (NCT02724540).

A more recent liver directed approach consists of embolization of ^{90}Y glass or resin microspheres to liver metastases. This approach is also known as selective internal radiotherapy (SIRT).[61] While initial data showed promising response rates and favorable short-term toxicities, long-term follow-up has demonstrated relatively high rates of radioembolization-induced liver disease which can lead to jaundice, ascites, and progressive hepatic dysfunction.[62]

SELECTION AND SEQUENCING OF THERAPIES

The development of randomized prospective studies has led to approval of multiple new drugs for various indications within the GEP-NET field (Table 1). In nearly all randomized studies, the control arm has consisted of a placebo or a non-standard treatment. As a result, there have been few studies comparing two active drugs, and absence of high-level evidence regarding selection and sequencing of treatments. At this time, some treatment recommendations can only be made based on cross-trial comparisons.

For nearly all well-differentiated SSTR-expressing GEP-NETs, first-line systemic treatment should consist of an SSA. This recommendation is endorsed by guidelines [63] and is based on the exceptional tolerability and safety of octreotide and lanreotide, as well as high level of evidence for their antiproliferative effect as demonstrated in the PROMID and CLARINET trials.

Treatment selection is more complicated beyond the first-line setting. For midgut NETs, high-level evidence exists for use of ^{177}Lu-dotatate based on the NETTER-1 study. There is weaker

evidence to support use of everolimus based on negative results from the RADIANT 2 study which enrolled primarily patients with hormonally functioning midgut NETs. Liver-embolization remains an important treatment modality for patients with liver-dominant midgut NETs, despite lack of high-level trial evidence. Use of radioembolization should probably be limited in this population, particularly in light of likely overlap in toxicity with ^{177}Lu-dotatate and potential for long-term radiation-induced liver disease.

For non-midgut GI NETs, evidence for use of everolimus is high, based primarily on results of the phase III RADIANT 4 study. However, outcomes with ^{177}Lu-dotatate based on single-arm data are also encouraging, and ultimately prospective clinical trials should compare radiolabeled SSAs to everolimus in this population. One such trial, the COMPETE study, is investigating everolimus versus ^{177}Lu-dotatoc in non-functioning SSTR-positive GEP-NETs, and should provide much needed data comparing efficacy and toxicity of two active treatment regimens (NCT03049189).

The systemic treatment options for progressive pancreatic NETs are even more diverse. High level evidence now supports use of everolimus, sunitinib, and capecitabine plus temozolomide, while single arm studies support use of ^{177}Lu-dotatate in this population.[64] Results of the ECOG 2211 study demonstrate median PFS of nearly 2 years in patients with progressive pancreatic NETs treated with capecitabine and temozolomide, an outcome unmatched in randomized clinical trials evaluating similar populations. Nonetheless, randomized clinical trials are needed to compare capecitabine/temozolomide to other standard regimens such as everolimus or sunitinib in order to begin to establish evidence-based treatment sequencing guidelines.

More data is also needed to establish predictive markers in order to appropriately match patients with treatments. At this time, PRRT is the only treatment with a predictive clinical biomarker: SSTR expression on somatostatin-receptor imaging. A predictive blood marker for ^{177}Lu-dotatate response has also been developed which should be validated in additional studies.[65] The role of MGMT expression for prediction of response to capecitabine/temozolomide will be evaluated in the ECOG 2211 study. Predictive markers for everolimus therapy, including mutations of mTOR pathway enzymes, have not been validated.

FUTURE DIRECTIONS

PRRT remains an important area of investigation for patients with GEP-NETs. Retrospective studies evaluating PRRT in select high-grade tumors have shown encouraging results, but prospective studies are needed. SSTR-antagonist (as opposed to agonist) based PRRT has been evaluated in several small, early phase studies with mixed results.[66, 67] New classes of isotopes, such as alpha-emitters, have only been evaluated in small institutional series, and formal prospective trials are needed to assess the efficacy of alpha-emitting radiolabeled SSAs.[68] Finally, the role of fixed-dose versus dosimetrically calculated administration of PRRT has yet to be evaluated in a randomized trial.

Other novel therapies also exploit high levels of SSTR expression in GEP-NETs. A miniaturized antibody-drug conjugate (ADC), PEN-221, has been developed for treatment of NETs, and phase II studies are ongoing (NCT02936323). Bispecific antibodies targeting SSTR2 and CD3 represent another novel form of therapy.[69] Finally, chimeric antigen receptor (CAR)-T cell technology targeting SSTR is in early phases of preclinical development.

Immunotherapy has radically altered the landscape of cancer treatment, but GEP-NETs appear to be relatively resistant to immunotherapy with PD-1 inhibitors, possibly due to their low mutational burden.[48, 49] Further studies evaluating inhibition of additional checkpoints as well as combination studies evaluating immune sensitizers are warranted. Studies evaluating the combination of PRRT with immunotherapy are currently open, but interpretation of results of single-arm studies may be difficult.

CONCLUSION

Medical treatment options for GEP-NETs have expanded dramatically in recent years. PRRT using ^{177}Lu-dotatate represents a novel treatment approach to SSTR-expressing tumors. Its use needs to be considered in appropriate patients within the context of the larger treatment landscape, and ideally evaluated by a multidisciplinary team of NET experts.

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Table 1: Key randomized prospective studies of therapies for GEP-NET

Drug category	Medication	Study	Population	Primary End Point	Primary End Point Results
Somatostatin analog	Octreotide LAR 30 mg every 4 weeks vs placebo	PROMID	Metastatic midgut NETs	Time-to-tumor progression	14.3 vs 6 months (HR, 0.34; P = .000072)
Somatostatin analog	Lanreotide 120 mg every 4 weeks vs placebo	CLARINET	Metastatic enteropancreatic NETs	PFS	Median PFS not reached vs 18 Months (HR, 0.47; P <.001)
Tryptophan hydroxylase inhibitor	Telotristat 250 mg 3 times a day vs telotristat 500 mg 3 times a day vs placebo	TELESTAR	Carcinoid syndrome	Change from baseline in BM frequency per day	–1.7 vs –2.1 vs –0.9 (mean BM reductions at week 12), (P <.001)
mTOR inhibitor	Everolimus vs placebo (both with octreotide LAR every 28 days)	RADIANT-2	Advanced NETs with carcinoid syndrome	PFS	16.5 vs 11.3 months (HR, 0.77; P = .026)
mTOR inhibitor	Everolimus vs placebo (both with best supportive care)	RADIANT-3	Advanced pancreatic NETs	PFS	11 vs 4.6 months (HR, 0.35; P <.001)
mTOR inhibitor	Everolimus vs placebo	RADIANT-4	Advanced nonfunctioning NETs of the lung or gastrointestinal tract	PFS	11 vs 3.9 months (HR, 0.48; P <.00001)
Anti-angiogenic	Sunitinib vs placebo		Advanced pancreatic NETs	PFS	11.4 vs 5.5 months (HR, 0.42; P <.001)
Cytotoxic chemotherapy	Temozolomide vs Temozolomide plus capecitabine	ECOG-ACRIN Cancer Research Group (E2211) trial	Advanced pancreatic NETs	PFS	22.7 vs. 14.4 months (HR = 0.58, p = 0.023)
PRRT	177 Lu-Dotatate plus	NETTER-1	Metastatic midgut NETs	PFS	Median PFS not reached vs

	octreotide LAR 30mg vs octreotide LAR 60 mg every 4 weeks				8.4 months (HR, 0.21; P <.0001)

BM: bowel movement; LAR: long-acting release; NET: neuroendocrine tumors; PFS: progression-free survival; mTOR: mammalian target of rapamycin; PRRT: Peptide Receptor Radionuclide Therapy