





# Peptide Receptor Radionuclide Therapy for the Treatment of Pancreatic Neuroendocrine Tumors: Recent Insights

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**Abstract:** Peptide receptor radionuclide therapy (PRRT) is a paradigm shifting approach to the treatment of neuroendocrine tumors. Although there are no prospective randomized trials directly studying PRRT in pancreatic neuroendocrine tumors (panNETs), there are data to suggest benefit in this patient population. Collectively, the data, consisting of two prospective and six retrospective studies, show a median PFS ranging from 20 to 39 months and a median OS ranging from 37 to 79 months. There are ongoing (and upcoming) prospective, randomized trials of PRRT in panNETs, which will provide further evidence to support this approach.

**Keywords:** pancreatic neuroendocrine tumor, panNET, peptide receptor radionuclide therapy, PRRT, theranostics

## Introduction

Effective therapies for gastroenteropancreatic neuroendocrine tumors (GEP-NETs) beyond first-line somatostatin receptor analogs (SSA) are limited. The introduction of peptide receptor radionuclide therapy (PRRT) has introduced a transformative treatment for patients with GEP-NETs. Approval of PRRT for GEP-NETs in the United States and Europe was primarily based on the NETTER-1 trial.<sup>1</sup> It is important to point out that the NETTER-1 trial enrolled patients with small bowel NETs only and did not include pancreatic neuroendocrine tumors (panNETs). To date, no randomized, prospective trials of PRRT in patients with panNETs have been reported but such trials are underway. Most of the evidence supporting PRRT for treating patients with panNETs derives from retrospective studies and small prospective Phase II trials.<sup>2</sup> This review is designed to highlight data for which PRRT has been used in panNETs.

## Pancreatic Neuroendocrine Tumors Biology

PanNETs belong to the diverse group of neuroendocrine neoplasms (NENs) that arise from neuroendocrine cells in the gastrointestinal tract.<sup>3</sup> Embryologically these tumors are of foregut origin and likely stem from specialized cells in the pancreas referred to as islet cells.<sup>4</sup> PanNETs are classified based on their grade (grade 1–3), morphologic differentiation (well differentiated vs. poorly differentiated), as well as whether the tumor is functional or non-functional.<sup>5</sup> Functional tumors can secrete hormones such as insulin, gastrin, glucagon, vasoactive intestinal peptide (VIP), and somatostatin.<sup>6</sup> As a result of

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excess hormone secretion, panNETs can be associated with a number of syndromes. The most common of these syndromes include insulinoma and Zollinger-Ellison syndrome (gastrin), while the less common include VIPoma (vasoactive intestinal peptide), glucagonoma, and somatostatinoma. The majority of panNETs are nonfunctional.<sup>7-9</sup>

PanNET grading is based on the proliferative rate of the tumor, which is determined based on Ki-67 and/or mitotic index. The latest installment of the WHO Classification of Tumours of Endocrine Organs updated panNETs to include a well-differentiated grade 3 subtype.<sup>5</sup> Additionally, the cut-off of Ki-67 was changed from <2% to <3% for grade 1 tumors. The grade of the tumor is helpful for determining prognosis and treatment approach, though clinical behavior and demonstrated pace of growth are important factors as well.

The genomic landscape of this disease has been investigated with next-generation sequencing.<sup>10-12</sup> Recurring somatic mutations were found to be predominantly in three molecular domains including chromatin remodeling factors (CRFs), histone methyltransferases (HMTs), and genes involved in the mTOR pathway.<sup>13</sup> The most common altered genes in one study were *MEN1*, *DAXX*, *ATRX*, and *TSC2*. Epigenetics has been another area of active investigation to help understand pathogenesis and predict the prognosis of panNETs.<sup>10,14</sup>

## Epidemiology

PanNETs are considered rare tumors with an incidence of <1 case per 100,000 individuals per year and represent 1% to 2% of all pancreatic neoplasms.<sup>15</sup> The incidence of these tumors has been increasing over the past 40 years from 0.27 to 1.00 per 100,000.<sup>16</sup> Additionally, patients are increasingly being diagnosed at earlier stages, likely as a result of improved diagnostic methods, namely imaging modalities (ie <sup>68</sup>Ga DOTATATE PET/CT, <sup>111</sup>In pentetreotide) and endoscopic techniques.<sup>3</sup>

The incidence of panNETs is generally comparable between males and females with an incidence of 0.72 and 0.51 per 100,000 patients for males and females, respectively.<sup>17</sup> The highest incidence of these tumors occurs in the third to sixth decade of life.<sup>5</sup> Most panNETs are sporadic in nature; however, 10–20% occur in the setting of an inherited syndrome such as multiple endocrine neoplasia type 1 (MEN1), von Hippel–Lindau (VHL) syndrome, neurofibromatosis type 1 (NF1), and tuberous sclerosis.

## Prognosis

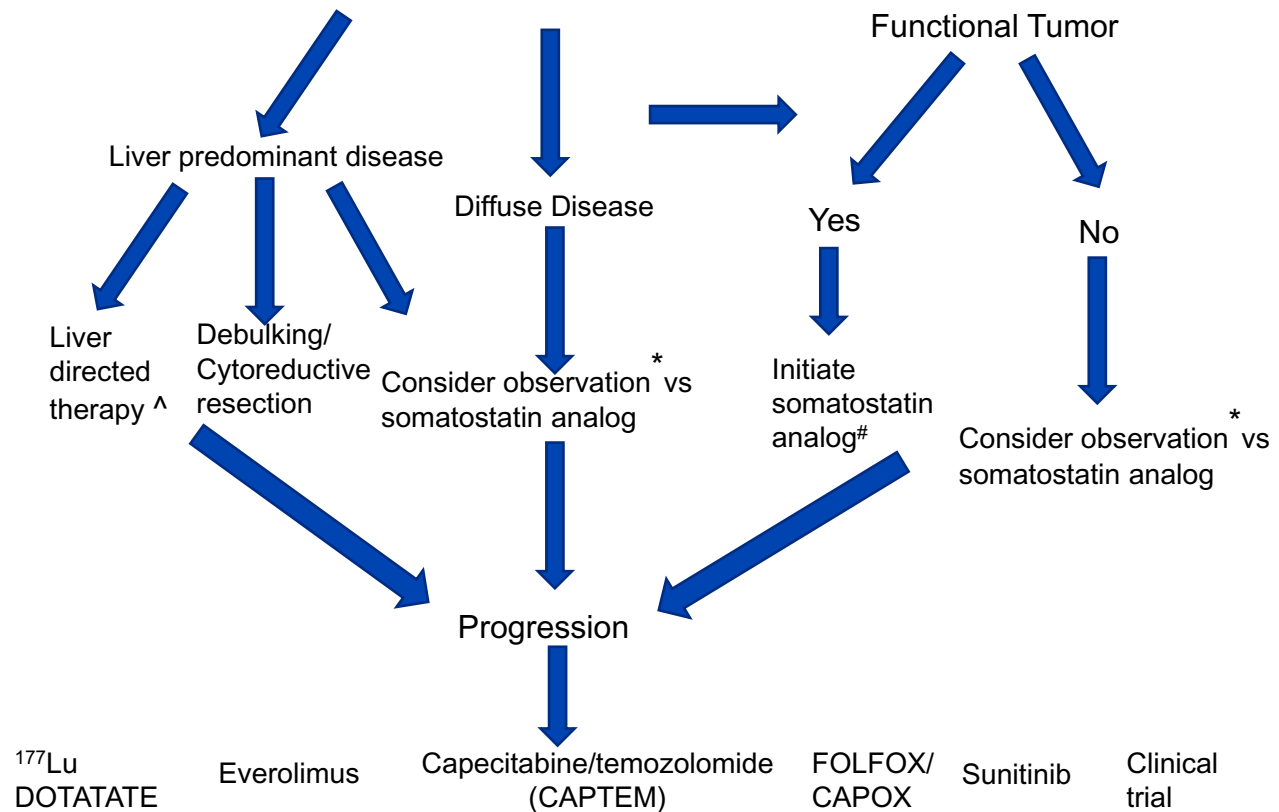
The prognosis of panNETs varies based on stage and grade of the tumor. Tumors <2 cm tend to have an excellent prognosis, reflecting an indolent biology/grade.<sup>18-21</sup> For localized tumors (stage I, II) amenable to resection >80% are cured by surgery alone.<sup>22</sup> For advanced (ie stage IV) disease, there has been significant improvement in the survival of grade 1 and grade 2 panNETs over the past three decades with an improvement of median overall survival from approximately 2 years to 5 years.<sup>16</sup> Advanced grade 3 panNETs have a less favorable prognosis, although much better than poorly differentiated (grade 3) pancreatic neuroendocrine carcinomas, with 5-year survival rates of 29%.<sup>23</sup> At present, there are several molecular markers of interest that may improve prognostication following surgery, most notably mutations in *ATRX* and *DAXX* and alternating lengthening of telomeres.<sup>4,24-27</sup>

## Treatment

The treatment of panNETs depends on symptom severity and etiology along with biology and tempo of disease. First-line treatment is typically determined by symptoms, disease bulk, pace of growth, along with disease distribution; specifically liver predominant disease versus diffuse disease (Figure 1). For liver predominant disease, a surgical debulking can be considered (typically if >70% of the disease can be removed) and/or liver directed therapies (eg radioembolization, bland embolization, chemoembolization) can be considered.<sup>28</sup> These interventions can be very helpful for symptom control as well. It is worth mentioning in the era of PRRT that there are limited data for the sequential use of PRRT and radioembolization (<sup>90</sup>Y). A study of 20 patients who received sequential PRRT (45% of whom received this first) and radioembolization showed no increased liver toxicity with either modality in either sequence.<sup>29</sup> Another study analyzed 23 patients who received radioembolization after PRRT and also saw no increased hepatotoxicity.<sup>30</sup> Despite this limited data, suggesting this is a safe approach; caution should be exhibited when using these modalities sequentially until further data are available.

For significant extra-hepatic disease, first-line treatments with somatostatin analogues (SSAs) (ie octreotide LAR, lanreotide) are used to treat hormonal syndrome and halt disease progression.<sup>31</sup> For more bulky, symptomatic disease, capecitabine with temozolomide may be beneficial.<sup>32-34</sup> The recent ECOG2211 was a prospective, randomized phase II trial that looked at temozolomide (TEM) vs capecitabine and temozolomide (CAPTEM) in advanced well-differentiated grade 1/

## Management Algorithm for Advanced Pancreatic Neuroendocrine Tumors (Grade 1-3)



**Figure 1** Algorithm for treatment of advanced panNETs.

grade 2 panNETs. CAPTEM when compared to single-agent TEM improved progression-free survival (PFS) 22.7 months (mo) vs 14.4 mo ( $p=0.023$ ), overall survival (OS) not reached vs 38 mo ( $p=0.012$ ), and overall response rate (ORR) 33.3% vs 27.8% ( $p=0.47$ ), respectively. Other therapies that can be considered for advanced panNETs include sunitinib and everolimus, both which have been shown to prolong PFS compared to placebo, but ORR is  $<10\%$  with these agents.<sup>35,36</sup> In January 2018, the peptide receptor radionuclide therapy (PRRT) Lutetium-177 Dotatate (Lutathera<sup>®</sup>) was FDA approved for the treatment of advanced somatostatin positive GEP-NETs. This was based on data from the prospective NETTER-1 trial in small bowel NETs and the retrospective Rotterdam, Netherlands experience.<sup>1,37</sup> It should be noted that NETTER-1 did not include panNETs, and the Netherlands experience at Erasmus included approximately 30% (91/310) panNETs in its phase II study.<sup>37</sup> NETTER-1 was a Phase III, prospective, randomized controlled trial that evaluated <sup>177</sup>Lu-DOTATATE combined with 30 mg long-acting repeatable (LAR) versus 60 mg octreotide LAR after first-line progression on SSA alone. <sup>177</sup>Lu-DOTATATE as compared to

octreotide LAR showed improvements in PFS 28.5 mo vs 8.5 mo, and ORR 18% vs 3%, respectively.<sup>38</sup> The OS data is still maturing.

### Role of Somatostatin Analogues

Central to identifying somatostatin as a potential target in GEP-NETs was the discovery by Jean Claude Reubi (Sandoz Research Institute), Steven Lamberts (Erasmus Medical Center), and Larry Kvolts (Mayo Clinic) of the presence of somatostatin receptors in the gastrointestinal tract in 1985.<sup>39</sup> Somatostatin is a naturally occurring hormone in the body with the highest concentrations in the gastrointestinal tract, pancreas, and central nervous system (especially the pituitary gland).<sup>40,41</sup> It normally acts as an inhibitory hormone, specifically regulating the release of gastrin, insulin, glucagon, pancreatic amylase, cholecystokinin, among others.<sup>42–45</sup> There are five different naturally occurring somatostatin receptors (SSTR 1–5) on neuroendocrine cells. SSTR2 has the highest expression in GEP-NETs, at approximately 80–90%, making this an attractive target.<sup>46</sup> Based on this finding the SSAs were developed to have the highest affinity for SSTR2.<sup>46</sup>

It has been known for many decades that SSAs decrease the neuropeptide/hormone overproduction, which accounts for carcinoid syndrome and cause a similar reduction in the production of hormones resulting in symptomatic improvement that has been seen in patients with functional panNETs.<sup>47–49</sup> In addition, somatostatin has inhibitory effects on cell proliferation which was further proven clinically with the CLARINET (lanreotide) and PROMID (octreotide long-acting release [LAR]) studies. In the CLARINET study, lanreotide vs placebo yielded a PFS of 32.8 months vs 18 months (95% CI, 30.9–68), respectively.<sup>31</sup> (PMID 2674312). The PROMID study, which notably excluded patients with panNETs, found a median PFS of 14.3 mo vs 6 mo in the octreotide LAR and placebo groups, respectively.<sup>31,50</sup>

## Biology of PRRT

The utility of PRRT in NETs rests on the biologic basis of somatostatin receptor expression on the surface of NETs. PRRT consists of a radionuclide (ie Lutetium-177 [<sup>177</sup>Lu], Yttrium-90 [<sup>90</sup>Y]) bound to a chelator (ie DOTA) which is attached to an SSTR ligand, such as [Tyr<sup>3</sup>] octreotate or [Tyr<sup>3</sup>] octreotide.<sup>51</sup> The compound is given intravenously and the ligand (ie [Tyr<sup>3</sup>] octreotate) binds to the SSTR on the cell surface and subsequently delivers β<sup>-</sup> radiation emission. The β<sup>-</sup> emission has a range of 2 mm for <sup>177</sup>Lu and 12 mm for <sup>90</sup>Y. Of note, <sup>177</sup>Lu also emits low-energy γ rays which may be of value in scintigraphic confirmation of dose delivery immediately after administration. Furthermore, there is an interest in serial imaging after therapy to calculate a residence time of radiotracer, which may in turn reflect treatment efficacy.<sup>52</sup> Of the studied compounds, there has been the most clinical experience with <sup>177</sup>Lu-DOTATATE and <sup>90</sup>Y-DOTATOC.

## Historical Perspective of PRRT (Figure 2)

With the development of the first synthetic somatostatin compound, octreotide (Bauer Life Science, Marchbach Pharm Biotechnology, 1998), there were soon attempts to couple this compound with a radioisotope, namely iodine [<sup>123</sup>I], because of early success with using this radioisotope in the treatment of thyroid disease.<sup>39</sup> The use of this compound gave us the first look at the potential of somatostatin expression as a theranostic. In 1990 Eric Krenning and colleagues developed <sup>111</sup>In-pentetreotide somatostatin scintigraphy (Octreoscan). Based on their experience with this imaging, the FDA approved (in 1994) <sup>111</sup>In-pentetreotide for the diagnostic imaging of GEP-NETs.<sup>53</sup> Again, mirroring

the experience in thyroid cancer with radioactive iodine, Krenning and his team were able to treat a patient with high doses of <sup>111</sup>In-pentetreotide; thus successfully delivering the first PRRT treatment in NETs.<sup>54</sup> This early work set the stage for the later development of more sensitive diagnostic imaging with <sup>55</sup>Ga-DOTATATE and ultimately identification of the radiopharmaceutical <sup>177</sup>Lu-DOTATATE. Studies with <sup>177</sup>Lu-DOTATATE started in 2000 in Rotterdam, Netherlands and led to the international Phase 3 trial, NETTER-1.

## PRRT in Pancreatic Neuroendocrine Tumors

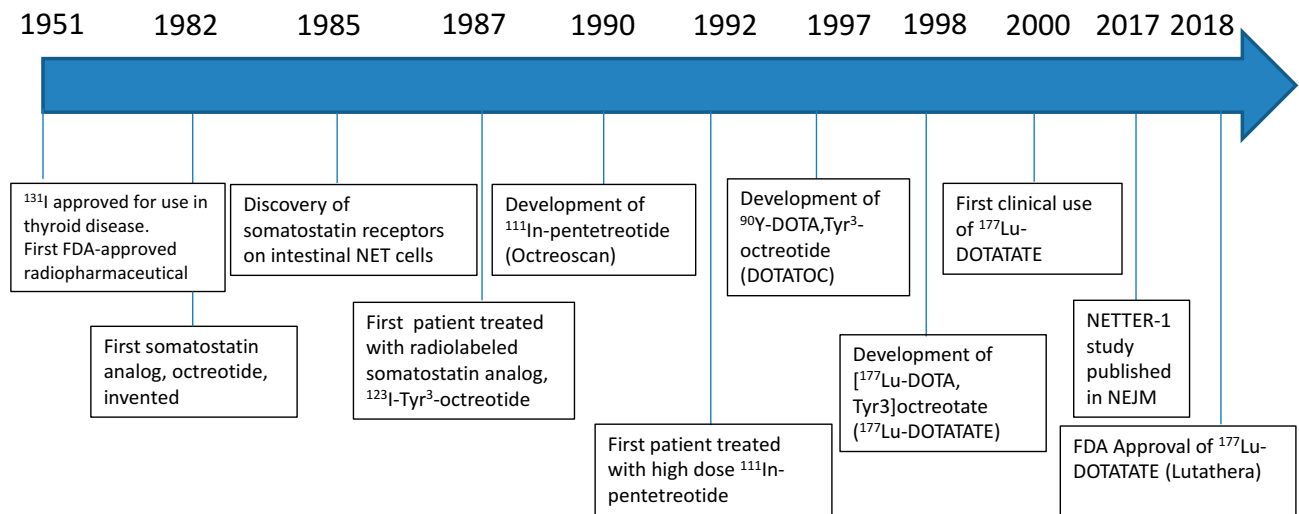
### Efficacy

#### <sup>177</sup>Lu-DOTATATE

It should be noted that there have been no randomized, prospective, Phase III trials utilizing PRRT in panNETs. Furthermore, the NETTER-1 trial which is the largest study utilizing PRRT did not include panNETs. However, there are data, both prospective and retrospective, examining the use of PRRT in panNETs.<sup>2</sup> The median disease control rate (DCR) was 83% (range, 50–94%) and the median objective response rate (ORR) was 58% (range, 13–73%).<sup>37,56–63</sup> The median PFS ranged from 25 to 34 months with a median OS of 42 to 71 months.<sup>30,37,57,60,61,64</sup>

A retrospective study of 74 patients with GEP NET showed that panNET patients had a higher ORR (modified SWOG criteria), 73% vs 39% (p=0.005). There was also a suggestion of longer median OS in panNET (57 vs 45 months); however, this was only noted univariate analysis (p=0.037) and not multivariate analysis (p=0.173).<sup>61</sup> In a study of 310 patients with GEP-NETs, the retrospective analysis revealed that those with functional panNETs had reduced disease-specific survival as compared to nonfunctional GEP-NETs, 33 months vs >48 months (p=0.04), respectively.<sup>57</sup> This was further supported by another retrospective study of 68 patients which showed that on univariate analysis functional panNETs had worse median OS than nonfunctional panNETs, 45 months vs 63 months (p=0.045), respectively; however, this finding did not hold statistical significance on multivariate analysis (p=0.506).<sup>59</sup>

This study also noted that the grade of the panNET predicted outcomes with PRRT. Grade 1 tumors had a median PFS of 45 months (95%, CI 35–55) as compared to 28 months (95%, CI 20–36) in patients with grade 2 tumors (p=0.04). In



**Figure 2** Historical evolution of peptide receptor radionuclide therapy.

addition to functionality and grade of the panNET, the presence of fluorodeoxyglucose (FDG) uptake on positron emission tomography (PET) was noted to be a prognostic factor.<sup>64</sup> A retrospective analysis of 60 patients identified that those with positive FDG PET had a median PFS of 21.1 months versus 68.7 months in those with a negative FDG PET ( $p < 0.0002$ ). This was also confirmed on multivariate analysis showing an HR of 5.15 (95% CI, 1.42–18.75;  $p = 0.13$ ) risk for progression with a positive FDG PET.

#### <sup>90</sup>Y-DOTATOC and <sup>90</sup>Y-DOTATATE

The largest experience utilizing <sup>90</sup>Y-DOTATOC was in a prospective phase II trial evaluating 342 patients with panNETs (functional,  $n = 47$ ; nonfunctional,  $n = 295$ ). Almost half of the patients with panNETs (ORR = 47%, RECIST criteria) experienced tumor response. The reported mean OS in the nonfunctional panNET group was 60 months.<sup>65</sup> The largest experience with <sup>90</sup>Y-DOTATATE in panNETs comes from a Phase 2 trial evaluating 30 patients.<sup>66</sup> In this group, the ORR was 39% with a median PFS and OS of 25 mo and 42 mo, respectively.

### Pooled Analyses of PRRT in panNETs

Collectively, a total of eight studies (2 prospective, 6 retrospective) reported outcomes of PRRT in panNETs (Table 1).<sup>55,67–73</sup> The reported median PFS ranged from 20 to 39 months and median OS ranged from 37 to 79 months. Of note, no significant difference in PFS or OS was found when comparing panNETs and other sites of NETs.<sup>71,72</sup> It should also be noted that these studies are

quite heterogeneous in terms of previous lines of therapy administered as well as whether patients had progressive disease when treated.

### Functional panNETs

Two studies evaluated PRRT for treatment of gastrinoma.<sup>69,74</sup> One of those studies evaluated 11 patients with gastrinoma and noted that all of the patients improved symptomatically; however, the mean survival was only 14 months.<sup>74</sup> The other study evaluated 36 patients with gastrinoma and showed an ORR of 30% along with a clinical response of 16%.<sup>69</sup> For those deemed responders, the median OS was 45 months. For malignant insulinomas, there is limited data in the form of case reports/series suggesting a benefit of PRRT in both stabilizing disease and hypoglycemia.<sup>75,76</sup> A recent retrospective study of 34 patients with metastatic functional pNETs and refractory hormonal symptoms found that the majority (71%) had a significant improvement in the functional syndrome and 80% had a reduction in the corresponding circulating hormone levels. After PRRT, the median PFS was 18.1 months and was associated with a concurrent increase in quality of life (QoL).<sup>77</sup> A similar but smaller study of 11 patients with refractory secretory symptoms was recently reported and most patients experienced symptomatic improvement following PRRT.<sup>78</sup> As an example, 4 of 5 patients with insulinoma and refractory hyperglycemia improved. Among the patients with symptomatic gastrinoma and glucagonoma, symptomatic improvement was not as consistent.



**Table 1** Efficacy of PRRT in panNET

Study	Radiopharmaceutical	Study Type	No. of panNET Patients	Response Criteria	ORR	mPFS Months (95% CI)	mOS Months (95% CI)
Baum <sup>55</sup>	<sup>177</sup> Lu-PRRT (36%), <sup>90</sup> Y-PRRT (15%) or both (49%)	Retrospective	384	RECIST	NS	20 (17–23)	44 (38–50)
Sharma <sup>73</sup>	<sup>90</sup> Y-PRRT (83%), <sup>177</sup> Lu-PRRT (15%)	Retrospective	35	Non-standard	NS	NS	37 (18–48)
Kunikowska <sup>72</sup>	<sup>90</sup> Y-DOTATATE & <sup>177</sup> Lu-DOTATATE	Prospective	19	RECIST	NS	30	79
Bertani <sup>71</sup>	<sup>90</sup> Y-DOTATOC (37%), <sup>177</sup> Lu-DOTATATE (28%), both (35%)	Prospective	90	RECIST	26%	36 (24–44)	75 (64–104)
Horsch <sup>70</sup>	<sup>177</sup> Lu-PRRT (54%), <sup>90</sup> Y-PRRT (17%), both (29%)	Retrospective	172	RECIST	NS	39 (29–49)	53 (37–69)
Dumont <sup>69</sup>	<sup>90</sup> Y-DOTATOC (80%) or <sup>90</sup> Y-DOTATOC & <sup>177</sup> Lu-DOTATOC (20%)	Prospective	36	NS	33%	NS	40
Campana <sup>68</sup>	<sup>90</sup> Y-DOTATOC or <sup>177</sup> Lu-DOTATATE	Retrospective	45	RECIST	31%	23	NS
Pfeifer <sup>67</sup>	<sup>90</sup> Y-DOTATOC (77%), <sup>177</sup> Lu-DOTATOC or both (23%)	Retrospective	21	RECIST	33%	27	NR

**Abbreviations:** PRRT, peptide receptor radionuclide therapy; panNET, pancreatic neuroendocrine tumor; ORR, overall response rate; mPFS, median progression-free survival; mOS, median overall survival; NS, not stated; NR, not reached; CI, confidence interval.

## Quality of Life (QoL) Measures

Very few studies have reported QoL measures in patients with panNET being treated with PRRT. The largest such study is a retrospective study in 68 patients with advanced panNET.<sup>79</sup> QoL was evaluated with the European Organization for Research and Treatment of Cancer – Quality of Life Questionnaire for Cancer patients, 30 items. Patients who received four cycles of PRRT did not have an adverse impairment of QoL in any measure. After 3 months from the last cycle of PRRT, it was noted that patients had significant improvement in global health status, social functioning, and symptoms of fatigue and appetite loss. These findings are consistent with a recent update regarding health-related QoL outcomes from the NETTER-1 trial as well as from the Erasmus group.<sup>77,80</sup>

## Safety

Overall, PRRT is a safe treatment and most adverse effects are transient. The nausea frequently seen following administration of the drugs has decreased substantially among patients receiving compounded nephroprotective arginine and lysine amino acid infusion as compared to commercially available amino acid solutions with more amino acids than arginine and lysine. Nephrotoxicity seems to be most frequently associated with PRRT using <sup>90</sup>Y and is virtually nonexistent when <sup>177</sup>Lu PRRT is given with nephroprotective amino acid infusion. Pooled analysis by Ramage et al reported on six studies that analyzed hematologic adverse events.<sup>2</sup> Two retrospective studies utilizing

<sup>177</sup>Lu-DOTATATE revealed a hematologic grade 3/4 AE rate of 5–7%, while the other four studies had no grade 3/4 hematologic adverse events.<sup>59,64,69,81–83</sup> This compares to a rate of 1–9% grade 3/4 hematologic AEs (mostly lymphopenia) in the NETTER-1.<sup>1</sup> In addition, permanent hematologic dysfunction has been reported in multiple studies with therapy-related myeloid neoplasms (t-MN) and bone marrow failures.<sup>1,55,84–87</sup> However, the incidence rates along with the clinical features of t-MN are variable across studies, ranging between 2% and 5%.<sup>1,37,57,60,65,72,84,87–104</sup> However, the majority of the studies have significant bias (selection bias, publication bias) due to their retrospective nature. Of note, the t-MN incidence in the PRRT group in the NETTER-1 trial was 0.9%.<sup>1</sup> However, the period of follow-up was short to accurately determine such risk. Prior studies have evaluated potential risk factors for developing t-MN after PRRT such as prior alkylating agents, metastatic disease to the bone, prior radiation, and others.<sup>84,87,90</sup> However, these factors have not been consistently implicated across studies.

## Future Directions

There is much work to be done with the future application of PRRT in panNETs. First, it is worth mentioning the soon to be opened NETTER-2 trial (NCT03972488) which is a phase 3, randomized, study with <sup>177</sup>Lu-DOTATATE with 30 mg octreotide LAR versus 60 mg octreotide LAR, in the first-line treatment of grade 2 and grade 3 advanced GEP-NETs.

Another study of interest is the COMPETE trial (NCT03049189) which is another phase 3, randomized, trial studying PRRT ( $^{177}\text{Lu}$ -DOTATOC) vs everolimus in the first-line treatment of advanced GEP-NETs (all grades included). Collectively the aforementioned somatostatin analogues, PRRT included, work in an agnostic fashion in binding of SSTR (namely SSTR2). Alternatively, there is a body of evidence that suggests that somatostatin antagonists, although not internalized into the cell, have improved binding capacity to SSTR and thus can potentially deliver higher doses of radiation to the tumor and provide improved theranostic-based imaging.<sup>105–107</sup> One theranostic grouping studied in clinical trials (NCT03773133, NCT 02592707) has two somatostatin antagonists, one for imaging,  $^{55}\text{Ga}$  – OPS202, and the other as the companion PRRT agent,  $^{177}\text{Lu}$ -OPS201 (satoretide).

Other potential strategies of interest are combining cytotoxic chemotherapy with PRRT. Investigators in Australia looked at 30 patients with grade 1 or 2 panNET and combined PRRT (4 doses of  $^{177}\text{Lu}$ -Dotatate) with CAPTEM (14 days of chemotherapy every 8 weeks during PRRT). This yielded an ORR of 80% with a median PFS of 48 months.<sup>108</sup> In Australia, the majority of patients receive 5-FU radiosensitizing chemotherapy with PRRT treatment.<sup>109</sup> A recent retrospective analysis from Australia revealed an incidence of t-MN as high as 4.8%, with 90% of the patients receiving chemotherapy with PRRT.<sup>85</sup> This highlights a word of caution regarding combining chemotherapy with PRRT and certainly more data are needed with this approach before being routinely employed.

In the era of immunotherapy, it is easy to foresee an approach that combines PRRT with immunotherapy (ie checkpoint inhibitors). Radiotherapy has been shown to increase tumor antigenicity as well as increase antigen presentation which in turn can enhance T-cell destruction of tumor cells.<sup>110</sup> Preclinical data of a NET xenograft model treated with PRRT showed increased infiltration of antigen-presenting cells and NK cells in the tumor microenvironment.<sup>111</sup> Studies employing a strategy of PRRT and immunotherapy are in development.

There are also questions that remain in terms of sequencing of therapy for panNETs. We have the ECOG2211 first-line data utilizing CAPTEM that showed impressive results in the treatment of this disease and it is unclear whether PRRT should be considered before or after. Additionally, as alluded to above it is unclear whether the sequencing of therapies increases the risk of t-MN. A trial looking at the sequencing of therapies would be important to help answer this question.

Another frontier that is being explored as it relates to PRRT is the use of alpha ( $\alpha$ ) particles, namely  $^{225}\text{Ac}$ tinium- and  $^{213}\text{Bi}$ smuth-DOTATOC therapy, as the radiation source.<sup>112</sup> The advantages of  $\alpha$  particle therapy include that they deliver radiation over a short range of emission (<0.1 mm) which helps spare damage to surrounding normal tissue.<sup>113</sup> Additionally, alpha radiation delivers a higher linear energy transfer than beta ( $\beta$ ) particles, thus can be more effective at inducing DNA double-strand breaks. Another such agent is  $^{212}\text{Pb}$ -DOTAMTATE completed a Phase I study with plans to open phase II in the near future. Alpha particle PRRT has the potential to usher in a new era in radiopharmaceuticals.

## Conclusion

While many therapies in the oncology as of late offer small, incremental benefits; PRRT has represented a true breakthrough in the treatment of NETs. Although prospective, randomized data with PRRT in panNETs are lacking, the data that we do have suggest this is an effective treatment for this disease, and absolutely warrants further investigation. Future efforts will be directed at enrolling patients on the clinical trials mentioned in this review (COMPETE and NETTER-2 trials) so that the medical community has stronger data to make treatment recommendations in panNET. Equally important will be the determination of sequencing of PRRT with the other therapies available, namely chemotherapy and immunotherapy. It will also be paramount to continue to assess long-term risks of PRRT, specifically the incidence of t-MN. Considering the caveats of the current data, PRRT represents an effective and promising therapy in the treatment of panNETs.

## Disclosure

Dr Timothy Hobday reports personal fees from Lexicon Pharmaceuticals, outside the submitted work. Dr Ayse Tuba Kendi was the principal investigator of Phase III VISION study in the treatment of metastatic castration-resistant prostate cancer patients with Lu-PSMA-617, at Mayo Clinic, outside the submitted work. Dr Thorvardur Halfdanarson reports grants that paid to the institution from Ipsen and Thermo Fisher Scientific; personal fees from Curium and Lexicon, during the conduct of the study. The authors report no other conflicts of interest in this work.

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