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REVIEW

The Role of Radioligand Therapy in Gastroenteropancreatic Neuroendocrine Tumors: An Italian Expert Opinion

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ABSTRACT

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) comprise a heterogeneous group of clinically diverse tumors; their management is based on clinical characteristics. International guidelines recommend standard-dose somatostatin analogues (SSAs) as first-line treatment for advanced, low-grade G1 and "low" G2 NETs. No standard-of-care treatment is determined for "high" G2 and G3 NETs. Radioligand therapy

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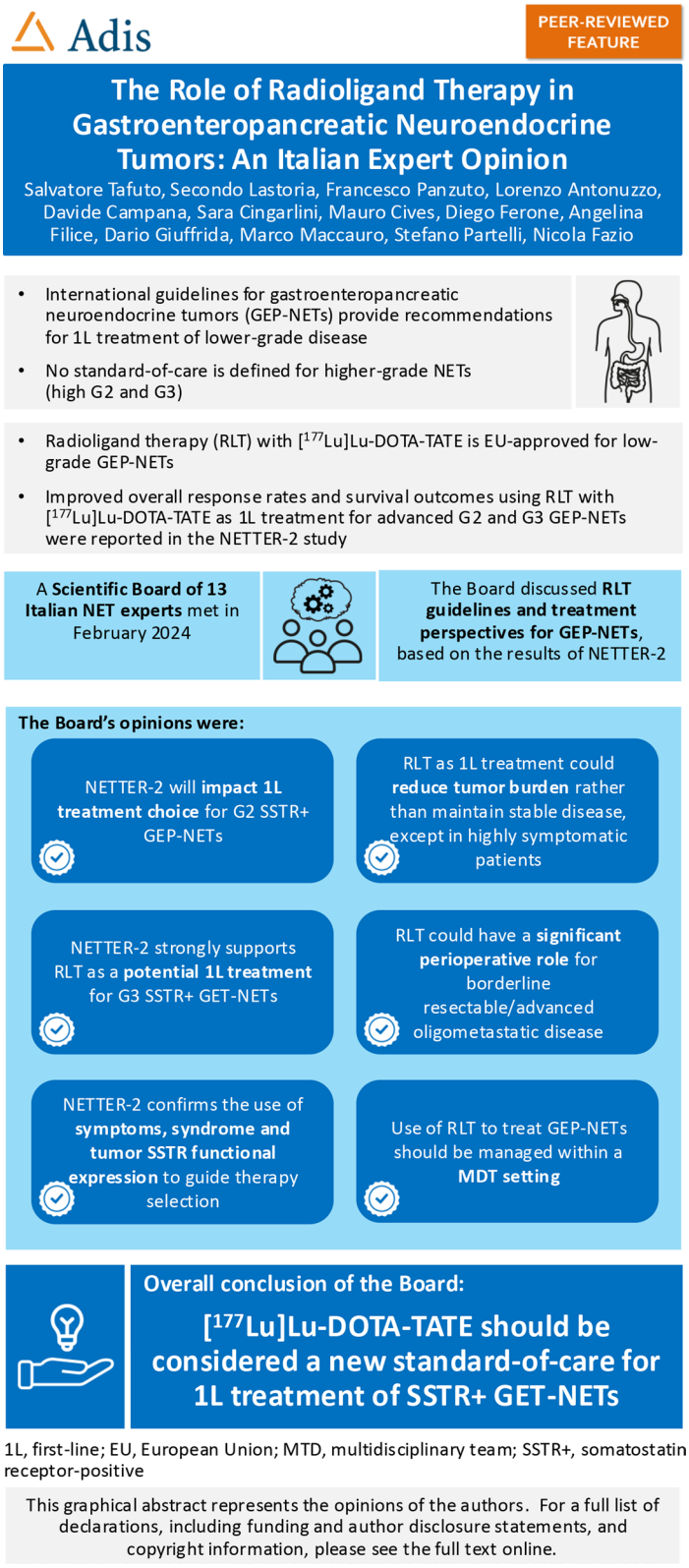
(RLT) with [^{177}Lu]Lu-DOTA-TATE was authorized to treat well-differentiated (G1 and G2) unresectable or metastatic, somatostatin receptor (SSTR)-positive GEP-NETs, in progression after SSA. Recently published NETTER-2 is the first randomized clinical trial to demonstrate the efficacy and safety of [^{177}Lu]Lu-DOTA-TATE as first-line treatment in patients with newly diagnosed, advanced "high" G2 and G3 GEP-NETs. In February 2024, 13 scientific board members discussed RLT guidelines and treatment perspectives in patients with GEP-NETs based on NETTER-2 outcomes. In their opinion, NETTER-2 will impact first-line treatment choice in patients with G2 SSTR-positive GEP-NETs. RLT as first-line treatment could reduce tumor burden rather than maintain stable disease, except in patients who are highly symptomatic where chemotherapy should be considered. In patients with G3 SSTR-positive GEP-NETs, NETTER-2 strongly supports RLT as potential first-line treatment. RLT could also have a significant role in a perioperative setting for those cases with borderline resectable disease or advanced oligometastatic disease. The results of NETTER-2 confirm that therapy selection should be guided by symptoms, syndrome, and functional expression of SSTR within the tumor site(s) rather than GEP-NET histology and grading. Thus, the scientific board agreed that RLT should always be considered in SSTR-positive GEP-NETs. Graphical Abstract available for this article.

Graphical Abstract:



1L, first-line; EU, European Union; MTD, multidisciplinary team; SSTR+, somatostatin receptor-positive

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Keywords: Expert opinion; Gastroenteropancreatic; GEP-NETs; NETTER-2; Neuroendocrine neoplasm

Key Summary Points

Radioligand therapy (RLT) with [^{177}Lu]Lu-DOTA-TATE has been authorized to treat well-differentiated (low-grade G1 and "low" G2) unresectable or metastatic, somatostatin receptor (SSTR)-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs) in progression after standard-dose somatostatin analogues (SSAs). However, no standard-of-care treatment has been established for "high" G2 and G3 NETs.

The NETTER-2 trial compared the efficacy and safety of RLT, specifically [^{177}Lu]Lu-DOTA-TATE plus octreotide long-acting repeatable (LAR) versus high-dose octreotide LAR, as first-line treatment in patients with newly diagnosed, well-differentiated, advanced G2 and G3 GEP-NETs.

The trial demonstrated a pronounced impact on overall response rates and survival outcomes, suggesting that [^{177}Lu]Lu-DOTA-TATE should be considered a new standard of care for the first-line treatment of this patient population.

The decision to use RLT to treat GEP-NETs should be managed within a multidisciplinary team setting on the basis of several factors, and should be guided by symptoms, syndrome, and functional expression of SSTR within the tumor site(s). NETTER-2 will impact first-line treatment choice in patients with G2 SSTR-positive GEP-NETs and RLT should always be considered in SSTR-positive GEP-NETs, where it could reduce tumor burden rather than just maintain stable disease.

DIGITAL FEATURES

This article is published with digital features, including a graphical abstract to facilitate understanding of the article. To view digital features for this article, go to https://doi.org/10.6084/m9.figshare.30166297.

INTRODUCTION

Neuroendocrine neoplasms (NENs) are rare and heterogeneous malignancies that arise from cells of the diffuse neuroendocrine system; therefore, they can develop in various anatomical sites of the body. The 2022 World Health Organization (WHO) classification [1] distinguished NENs as well-differentiated (neuroendocrine tumors, NETs) and poorly differentiated (neuroendocrine carcinomas, NECs). Immunohistochemistry for Ki-67/MIB-1 is mandatory to grade NENs by counting at least 500 cells in areas of highest labeling [2, 3]. On the basis of the Ki-67 index and mitotic rate, NETs are defined as grade (G)1 (Ki-67 < 3% and/or mitotic count < 2/2 mm^2), G2 (Ki-67 3–20% and/or mitotic count 2–20/2 mm^2), or G3 (Ki-67 > 20% and/or mitotic count > 20/2 mm^2); NECs, which constitute only 10–20% of all NENs, are, by definition, G3 and are separated into small- and large-cell types [1–4].

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are managed on the basis of their clinical characteristics. The heterogeneous presentation of GEP-NETs and the complexity of available therapeutic options necessitate a coordinated, multidisciplinary approach for their optimal management, which has been shown to improve the quality of care for patients with NETs [5, 6]. However, reflecting regional considerations and the heterogeneity of the disease, there is considerable inconsistency between the various published guidelines [7]. While international guidelines recommend standard-dose somatostatin analogues (SSAs) as first-line treatment for advanced, low-grade G1 and "low" G2 NETs, there is no universally accepted first-line treatment for high G2 and G3 GEP-NETs. The recently published results of the phase 3 NETTER-2 study have provided evidence of the value of a ^{177}Lu-labelled somatostatin analogue that binds to somatostatin receptors, [^{177}Lu]Lu-DOTA-TATE, as first-line

treatment in patients with advanced GEP-NETs [8]. [^{177}Lu]Lu-DOTA-TATE plus octreotide long-acting repeatable (LAR) significantly extended median progression-free survival, and has been proposed as a new standard of care for first-line therapy in this patient population [8].

This article discusses treatment perspectives of radioligand therapy (RLT) with [^{177}Lu]Lu-DOTA-TATE in patients with advanced GEP-NETs, based on the expert opinions of an Italian scientific board of NET experts who met to discuss the current guidelines and treatment perspectives for RLT in advanced GEP-NETs in the light of the NETTER-2 data, with the aim of supporting an update of the Italian guidelines.

GASTROENTEROPANCREATIC NEUROENDOCRINE TUMORS (GEP-NETS)

NETs originating from the gastrointestinal tract (stomach, small intestine, colon, rectum, appendix) or pancreas, known as GEP-NETs, are the most common. GEP-NETs are heterogeneous and characterized as functional or non-functional on the basis of the presence or absence of a clinical syndrome related to bioactive substances produced and secreted by the tumor [9].

NETs frequently express somatostatin receptors (SSTRs) at high density on their cell membranes [10]. Five SSTR subtypes (SSTR1–5) are described, with SSTR2 the most frequently expressed subtype in GEP-NETs, followed by SSTR5 [11, 12]. SSTR2 expression has been shown to be significantly higher in G1 and G2 NETs than G3 NETs ($p<0.0001$) [13]. These receptors can be targeted for both imaging and treatment with radiolabeled somatostatin peptide analogues including gallium-68 (^{68}Ga) a β+ emitter, for PET imaging, and lutetium-177 (^{177}Lu) a β– emitter for therapy [14–16].

Disease Epidemiology

The global incidence and prevalence of GEP-NETs is increasing [17]. Data from the Surveillance, Epidemiology, and End Results (SEER) database showed an increasing annual incidence of GEP-NETs from 2004 to 2015, with the highest incidence in patients aged 50–54 years [18]. In Europe, the prevalence ranges from 2.1 to 6.6 cases of GEP-NETs per 100,000 inhabitants [19]. In the USA, there is an increasing incidence rate of GEP-NETs in older populations, with an annual percent change of approximately 4–5% per year from 1975 to 2012 in patients aged 40–74 years [20]. In order to gather prospective data on the epidemiology, clinical attributes, and treatment strategies of newly diagnosed GEP-NENs in Italy, the Italian Association for Neuroendocrine Tumors (ITANET) initiated a national database in 2019 that includes patients from 37 centers, with data from 1600 patients recorded as of October 2023 [21] and an anticipated inclusion of 3600 patients by the end of 2025. The protocol has been registered in clinicaltrials.gov (NCT04282083).

Distinguishing between G3 NETs and NECs can be challenging, leading to their misclassification. Frequent use of outdated versions of the WHO classification has led to discrepancies in data, with G3 GEP-NETs commonly considered NECs as a result of the 2010 WHO classification, which exclusively assigned G3 tumors to NECs, and misuse of the term NETs to describe NENs [9]. Hence, pathological markers for the differential diagnosis of pancreatic (Pan)-NETs and Pan-NECs, such as p53, Rb1, ATRX, and DAXX, are essential [22].

Management

GEP-NETs have different clinical manifestations. Their management varies according to clinical characteristics and is best overseen by a multidisciplinary approach in dedicated expert centers.

The relatively indolent nature of a significant proportion of GEP-NETs has resulted in surgery being accepted as the treatment of choice for localized or locoregional disease, and radical surgery may be a curative approach when feasible in non-advanced disease. Systemic treatments in metastatic/non-resectable SSTR-positive disease include SSAs, targeted therapies, radioligand therapy (RLT), also known as peptide receptor

radionuclide therapy (PRRT), and chemotherapy [23–25].

The radiopharmaceutical/radioligand [^{177}Lu]Lu-DOTA-TATE (Lutathera®), composed of octreotate (a SSA), DOTA (a chelating molecule), and a β-emitting radioisotope (^{177}Lu), delivers therapeutic doses of β-radiation to SSTR-expressing NETs [26]. The European Medicines Agency (EMA) approved [^{177}Lu]Lu-DOTA-TATE for the treatment of unresectable or metastatic, progressive, well-differentiated (G1 and G2), SSTR-positive GEP-NETs in adults in 2017 [27], and it is now approved in more than 20 countries worldwide [28].

GEP-NENS: RLT IN TREATMENT GUIDELINES AND CLINICAL PRACTICE

A recent review on the management of non-functional Pan-NETs highlighted heterogeneity among international guidelines, with discrepancies concerning the general approach, therapy sequence, and options reported [7]. Consequently, the authors emphasized that guidelines should not be used verbatim but as a general tool to support the therapeutic decision-making of a multidisciplinary team for complex and tailored treatments.

The European Society for Medical Oncology (ESMO) 2020 GEP-NEN guidelines [4] recommend that diagnostic and therapeutic decisions should be based on proliferative activity, SSTR expression, tumor growth rate, and disease extent. In advanced/metastatic disease, systemic treatments aim to control tumor-associated clinical symptoms and tumor growth. In SSTR-positive NETs with carcinoid syndrome (most commonly flushing and/or diarrhea), SSAs are recommended as first-line therapy, with RLT as second-line therapy in patients with tumor progression. However, as remarked in the ESMO guidelines [4], "PRRT may be considered in patients without prior tumor progression but with high tumor burden and uncontrolled diarrhea (off-label)." In SSTR-positive midgut G1/G2 NETs and Ki-67 < 10%, RLT is recommended as second-line therapy after failure of SSA, while in patients with midgut G2 NETs and Ki-67 > 10–15%, RLT is recommended as second-line therapy after failure of everolimus [4]. ESMO guidelines also recommend RLT in Pan-NETs after the failure of other therapeutic options but state that "One author (EPK) indicates that in SSTR-positive Pan-NET G1/G2 (Ki-67 < 10%) PRRT might be considered after first-line SSA or chemotherapy, equal to the choice of targeted drugs and that in SI NET G2 (Ki-67 > 10%) PRRT could be considered equal to everolimus".

The ESMO GEP-NEN guidelines were last updated in 2020; a revision is pending. Recent studies support the earlier use of RLT in patients with enteropancreatic-NETs and disease progression on SSA treatment [29], with better progression-free survival (PFS) on RLT than other therapeutic strategies in both first- and second-line therapy settings in patients with advanced well-differentiated Pan-NETs [30].

In 2023–2024, the European Neuroendocrine Tumor Society (ENETS) developed several guidance papers written by a multidisciplinary consensus task force to provide practical clinical guidance on the diagnosis, treatment, and patient follow-up for different NENs [31–36]. These guidelines are, however, fragmented and nonhomogeneous, particularly for therapeutic sequences.

In the ENETS guidance paper for carcinoid syndrome [31], RLT is considered a therapeutic option not only for progressive tumors but also for stable disease when the carcinoid syndrome appears refractory to ongoing SSAs.

ENETS guidance for pancreatic tumors is separated into functioning and non-functioning (NF) NETs [35, 36]. In functioning Pan-NETs, RLT is recommended for gastrinoma, insulinoma, VIPoma, and glucagonoma in advanced cases progressing on SSAs [35]. RLT may be considered as second-line treatment in advanced G1-G2 NF-Pan-NETs with positive somatostatin-receptor imaging [36]. RLT is also recommended in the treatment of NF-Pan-NET G3 with high SSTR expression within clinical trials, with post hoc analyses showing significantly prolonged median PFS with RLT versus SSA regardless of baseline liver tumor burden [37]. Although several treatment lines

are available for SSTR-positive NF-Pan-NET, the optimal sequence of treatment lines, including RLT, is undefined [36].

In unresectable metastatic colorectal NETs [32], RLT is recommended as first-line treatment for tumors that are SSTR-positive, symptomatic, high tumor burden, rapid growth, and Ki-67 > 10% in the treatment options summarized in Fig. 2 of the ENETS guidance paper. However, there is a discrepancy between Fig. 2 and the ENETS recommendation, which states, "PRRT is recommended for SST positive metastatic colorectal NET progressing after prior treatment(s) although further data are needed").

The Italian Association of Medical Oncology (AIOM)/ITANET guidelines for NETs [38] have two theoretical advantages over the aforementioned guidelines. First, they derive from a close collaboration of disease-based and oncological scientific societies, and second, they are based on rigorous methodology (GRADE = Grading of Recommendations Assessment, Development and Evaluation). However, their utilization could be hindered by the fact that they are not yet published in a peer-reviewed journal. These guidelines are being updated, and algorithms will be available soon [39].

As a result of variance amongst guidelines, a standard timing of RLT in treatment algorithms of patients with NET remains controversial, and the profile of the perfect patient most likely to benefit from this therapy is unresolved [40]. The development of a diagnostic–therapeutic care pathway that provides systematic guidance individualized to the patient's specific clinical circumstances is recommended [41].

FROM CURRENT STATE OF THE ART TO THE FUTURE SCENARIO

EMA approval of [^{177}Lu]Lu-DOTA-TATE [27] was based on data from the retrospective cohort Erasmus Medical Center study in patients with Pan-NETs and the phase 3 NETTER-1 trial in patients with advanced, progressive, SSTR-positive midgut NETs [15, 16]. In NETTER-1, a markedly longer PFS was reported for [^{177}Lu]Lu-DOTA-TATE compared with the control arm with high-dose octreotide LAR. In updated post hoc analyses, the median PFS in patients treated with [^{177}Lu]Lu-DOTA-TATE was significantly longer than controls (28.4 vs. 8.5 months; HR 0.21 [95% CI 0.14, 0.33]; $p < 0.001$) (Table 1) [42]. However, G3 GEP-NET and newly diagnosed advanced or metastatic tumors were missing in the setting of NETTER-1 because, at the time of study design, the 2010 WHO classification of tumors of the digestive system [43] did not include G3 GEP-NET tumors. These tumors were first included in the 2017 WHO classification [2].

The long-term efficacy, survival, and safety of [^{177}Lu]Lu-DOTA-TATE were also demonstrated in a non-randomized study of 610 patients with G1 and G2 GEP-NETs and bronchial NETS [16]. Specifically, this study reported a median PFS of 29 months (95% CI 26–33 months) and overall survival (OS) of 63 months (95% CI 55–72 months), with few long-term severe adverse effects. The real-world effectiveness of [^{177}Lu]Lu-DOTA-TATE in patients with GEP-NET is also under investigation in an Italian, multicenter, long-term observational study (REAL-LU) [44]. In a planned interim analysis of REAL-LU, G2 GEP-NETs (Ki-67 index 3–20%) were identified in 70.9% of 86 patients evaluated for tumor grade at study entry, while 27.9% had G1 (Ki-67 < 3%) [44].

Most major international guidelines recommend standard-dose SSAs as first-line treatment for advanced, low-grade G1 and G2 NETs with low proliferation index. No standard-of-care treatment is determined for high-grade G2 and G3 NETs, highlighting the urgent need for treatment options in these patients.

Several retrospective cohort studies support RLT in the G3 GEP-NET setting. PFS and OS rates were favorable in a retrospective cohort analysis of 149 patients with G3 GEP-NEN treated with RLT as first-, second-, or later-line treatment, with an acceptable level of toxicity reported [45]. In this study, patients with well-differentiated G3 GEP-NENs had significantly better PFS (19 vs. 8 months) and OS (44 vs. 19 months) than those with poorly differentiated G3 GEP-NENs (both $p < 0.001$). In the retrospective SEPTRALU study, [^{177}Lu]Lu-DOTA-TATE was effective in patients with SSTR-positive GEP-NETs, with stable disease and partial response reported in patients with

Table 1 ORR, PFS, and OS in patients with GEP-NETs according to different treatment lines and grading

	ORR	Median PFS (months)	Median OS (months)
G2/G3 GEP-NETs (NETTER-2) [8, 51]			
RLT + SSA	43.0%	22.8 (95% CI 19.4–NE)	–
SSA	9.3%	8.5 (95% CI 7.7–13.8)	–
G1/G2 midgut NETs (NETTER-1) [42, 53]			
RLT + SSA	–	28.4	48.0 (95% CI 37.4–55.2)
SSA[a]	–	8.5	36.3 (95% CI 25.9–51.7)
G1/G2 pNETs [30]			
SSA	9.1%	9.7 (95% CI 6.9–12.5)	–
SSA + RLT	37.1%	34.3 (95% CI 27.3–41.2)	–
TMZ-based chemotherapy	31.6%	9.1 (95% CI 10.2–17.6)	–
SSA + TT	0%	10.1 (95% CI 7.3–12.9)	–
G1/G2 midgut NETS or pNETs (CLARINET FORTE) [62]			
SSA in G1/G2 midgut NETs	–	8.3 (95% CI 5.6–11.1)	–
SSA in G1/G2 pNETs	–	5.6 (95% CI 5.5–8.3)	–
pNETs [63]			
Sunitinib	–	12.6	38.6 (range 25.6–56.4)
G1/G2 pNETs (RADIANT-3) [64, 65]			
Everolimus	–	11.0 (95% CI 8.4–13.9)	44.0 (95% CI 35.6–51.8)
G1/G2 GI NETs or lung (RADIANT-4) [66]			
Everolimus	–	11.0 (95% CI 9.2–13.3)	–
G1/G2 pNETs [67]			
TMZ-based chemotherapy	33.7%	15.1 (95% CI 10.5–21.0)	53.8 (95% CI 35.7–NA)
CAP + TMZ-based chemotherapy	39.7%	23.2 (95% CI 16.6–32.2)	58.7 (95% CI 44.7–NA)

CAP capecitabine, *G* grade, *GI* gastrointestinal, *NA* not available, *NE* not estimated, *NETs* neuroendocrine tumors, *ORR* objective response rate, *OS* overall survival, *pNETs* pancreatic NETs, *PFS* progression-free survival, *RLT* radioligand therapy, *SSA* somatostatin analogues, *TMZ* temozolomide, *TT* targeted therapy

[a]Crossover was allowed

G3 GEP-NETs [46]. Conversely, PFS was not significantly higher with upfront RLT over chemotherapy or targeted therapy in patients with G3 enteropancreatic-NETs or when Ki-67 was > 10%, and the optimal sequencing of therapy remains to be determined [29, 47].

International guidelines also consider RLT as a reasonable treatment option in G3 GEP-NETs. In particular, the North American Neuroendocrine Tumor Society (NANETS) [48] guidelines state, "Based on consensus, it is reasonable to consider PRRT in patients with progressive G3 NET showing homogeneously high (avidity greater than liver) SSTR expression by imaging". The American Society of Clinical Oncology (ASCO) [49] guidelines position is that "The range of

systemic options recommended for G1 or G2 NETs may be recommended for well-differentiated G3 GEP-NETs, with treatment decision-making based on patient characteristics such as rate of proliferation, symptoms, tumor burden, and rate of growth". The ENETS 2024 guidance paper for the management of well-differentiated small intestine NETs (Si-NETs) now includes RLT as an option for first-line treatment in selected SSTR-positive G2 and G3 Si-NETs based on NETTER-2 study results [50].

However, as a result of the limited evidence and absence of randomized phase 3 clinical data, a universally accepted first-line treatment for patients with higher grade, well-differentiated GEP-NETs is lacking, and an unmet medical need prevails.

NETTER-2

The phase 3 NETTER-2 study (NCT03972488) evaluated [^{177}Lu]Lu-DOTA-TATE as first-line treatment in patients (aged ≥ 15 years) with newly diagnosed (within 6 months prior to enrolment), SSTR-positive, high G2 and G3 (Ki-67 ≥ 10% and ≤ 55%), well-differentiated, advanced GEP-NETs. The results of this international, multicenter, randomized, parallel-group, superiority, open-label study were initially presented at ASCO GI 2024 [51] and have been recently published [8].

Patients had to have stable disease evaluated by CT scan within 1 month before randomization. Patients who had received prior systemic treatments with RLT were excluded. Patients were randomized to receive four cycles of [^{177}Lu]Lu-DOTA-TATE (4 × 7.4 GBq) plus 30 mg octreotide LAR at 8-weekly intervals (treatment arm) or high-dose octreotide 60 mg LAR every 4 weeks (control arm). Re-treatment ([^{177}Lu]Lu-DOTA-TATE group) or crossover (control group) was allowed in patients with confirmed disease progression.

Overall, 226 patients were enrolled from nine countries and 45 centers (treatment arm: 151 patients, 78 patients still on treatment; control arm: 75 patients, 15 patients still on treatment). The two treatment arms were well balanced in terms of patient age, sex, and tumor status. G3 tumors were reported in 35% of patients: treatment arm (66% G2, 34% G3) versus control arm (64% G2, 36% G3). The median range of Ki-67 expression was 17%. The primary tumor site was predominantly pancreatic (54%), followed by the small intestine (29%). This differs from NETTER-1, which did not include pancreatic tumors. The principal site of metastasis was the liver, followed by lymph nodes and bone. Most patients in the treatment arm (88%) completed all four treatment cycles.

[^{177}Lu]Lu-DOTA-TATE as first-line treatment significantly improved PFS (primary endpoint met) versus high-dose octreotide LAR alone (22.8 vs. 8.5 months) (stratified hazard ratio 0.28 [95% CI 0.182, 0.418; $p < 0.0001$]), corresponding to a 72% risk reduction of disease progression or death. PFS results were consistent across all pre-specified subgroups.

The objective response rate (ORR) (key secondary endpoint) was significantly higher in the treatment arm than in the control arm (43.0% vs. 9.3%) (stratified odds ratio 7.81 [95% CI 3.32, 18.40; $p < 0.0001$]). Similarly, partial response (PR) was 38% versus 9%, and complete response (CR) was 5% versus 0%. ORR was found not only to be higher than that observed in NETTER-1 (43% vs. 19%) but also to be a significant figure in the oncological setting [50, 52].

Quality of Life (QoL) was similar in both treatment arms, and no new or unexpected safety findings were reported, in line with the established safety profile of [^{177}Lu]Lu-DOTA-TATE. Adverse events during the randomized treatment period were similar overall between groups (93% with [^{177}Lu]Lu-DOTA-TATE vs. 95% for controls [octreotide LAR]). The most common events were nausea (27% vs. 18%), diarrhea (26% vs. 34%), and abdominal pain (18% vs. 27%). A total of 35% of the ^{177}Lu-Dotatate group had adverse events of grade ≥ 3, with decreased lymphocyte count the most common (5% vs. 0), increased gamma-glutamyltransferase (5% vs. 3%), small intestinal obstruction (3% vs. 0), and abdominal pain (3% vs. 4%). There was one case of myelodysplastic syndrome (MDS) in the [^{177}Lu]Lu-DOTA-TATE group at approximately 14 months from the first dose.

NETTER-2 is strengthened by its study design, management, feasibility, and clinician involvement. Notably, the patient population is an extension of the clinical setting, with the inclusion of patients with G3 GEP-NET, a high number of pancreatic tumors, and uniformity in terms of Ki-67 expression. The control arm is also in line with NETTER-1. In terms of efficacy and safety outcomes, the positive response rate, with significantly higher PFS and ORR for [^{177}Lu]Lu-DOTA-TATE than high-dose octreotide LAR alone, alongside confirmation of the known safety profile of [^{177}Lu]Lu-DOTA-TATE in this patient population, adds to its strengths. Ultimately, NETTER-2 is the first clinical trial evidence to support the use of [^{177}Lu]Lu-DOTA-TATE as first-line treatment in patients with G3 GEP-NET. NETTER-2 is also the first study to allow re-treatment in patients with disease progression on [^{177}Lu]Lu-DOTA-TATE, otherwise termed "RLT rechallenge." The results of this RLT rechallenge will support the use of RLTs for a second treatment when the first has been successful for a period not inferior to 6–9 months.

In terms of its weaknesses, the NETTER-2 G3 population could not be representative of the real-life GEP-NET G3 population. The control arm only considered SSA, which may not be considered the optimal comparative therapy in G3, where it is plausible that in some cases, everolimus, sunitinib, or, more likely, chemotherapy is proposed despite a [^{68}Ga]Ga-PET uptake. It is anticipated that future comparative studies will address the issue of the most appropriate comparator. However, it is noted that maintaining SSA during RLT in NF NETs is a common practice based on clinical trial experience and possible synergies. It should also be emphasized that currently no reference therapy has been defined for G3 NETs, especially when extra-pancreatic. Also, the interval between doses may not be the most suitable and could be questioned, considering the rapid response of high-grade tumors. In the control group, patients with disease progression were able to crossover to treatment with [^{177}Lu]Lu-DOTA-TATE; although this is a weakness in terms of data immaturity and confounding of overall survival data, it also represents an advantage for the patients. More patients in the [^{177}Lu]Lu-DOTA-TATE group developed grade ≥ 3 lymphopenia than in the control group, and a longer follow-up will be more reliable regarding potential late bone marrow toxicity. No imaging data are available from NETTER-2; however, these are planned.

At present, long-term toxicity data for [^{177}Lu]Lu-DOTA-TATE in this setting are limited. As experience is accumulated, long-term data on both effectiveness and toxicity will emerge. This is likely to originate from the USA, where the first-line use in NETs has been available the longest.

During the 5-year follow-up period to NETTER-1, no new safety signals related to RLT were reported [53]. Serious adverse events of grade 3 or greater were reported in 6% of patients in the [^{177}Lu]Lu-DOTA-TATE arm during the entire study; 3% during the long-term follow-up period. These were mostly hematological or gastrointestinal events, hyperglycemia, or hypokalemia. Myelodysplastic syndrome developed in 2.3% of patients receiving RLT (and in no patients in the control group) in NETTER-1 during a median follow-up of 76 months and in ERASMUS 2% developed MDS and 0.5% acute leukemia during a median follow-up of 29 months [53, 54]. There were no new cases of MDS during long-term follow-up. During a median follow-up of over 4 years with ERASMUS, other serious adverse events occurred in no more than 2% of patients and included renal failure, hypotension, cardiac failure, myocardial infarction, and neuroendocrine hormonal crisis [54].

EXPERT MEETING: ACT EARLY

A multidisciplinary scientific board of 13 NET experts (coauthors of this paper) met on February 20, 2024, in Milan, Italy. Communication within the group was facilitated using the Metaplan method to promote a common understanding and formulate recommendations and action plans. This visualization-based facilitation technique enables participants to achieve a shared vision while considering all participants' views, guided by an independent facilitator. The purpose of the meeting was to discuss guidelines

and treatment perspectives for RLT in patients affected by advanced GEP-NETs based on data from NETTER-2. Participants were invited to interact freely, express opinions based on personal experience, and give their consent, or not, regarding all key messages that emerged during the meeting. The importance of not forcing a uniform conclusion but rather having a uniform approach to reasoning and addressing the questions was paramount. Under the Metaplan method, no structured search strategy is applied for identifying and selecting supporting references. Instead, the group's expertise and knowledge of the area are drawn upon, supplemented by reference to the relevant published literature.

A professional medical writer developed a draft manuscript based on minutes from the Metaplan discussions. The authors further developed and finalized the manuscript.

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

EXPERT OPINION

Can RLT + SSA Be Used as First-Line Treatment in Patients with G2 SSTR-Positive GEP-NETs?

The results of NETTER-2 will impact the decision-making process for choosing the first-line treatment in patients with G2 SSTR-positive GEP-NETs, particularly pan-NETs. In addition, the criteria for choosing a treatment should be reconsidered. Grading remains a prognostic factor and may be used to guide treatment choice; SSTR functional expression within the tumor sites (^{68}Ga-PET rather than immunohistochemistry) will drive the decision to use RLT.

The Ki-67 value should not be interpreted in an absolute manner in clinical practice for decision-making. Although it has a validated role in classifying GEP-NETs in terms of prognosis, its predictive role in therapy based on a specific cutoff is less clear.

To date, unfortunately, the indication in the first line of ^{177}Lu-DOTATATE for G2-G3 GEP-NET is approved in the USA only [55]. However, the results of NETTER-2 suggested that in "high" G2, RLT was more effective than SSA as first-line, and it cannot be excluded that it could be the same in "low" G2.

A recent position paper from the ITANET, Italian Association of Nuclear Medicine (AIMN), Italian Society of Endocrinology (SIE), and AIOM notes that "In the future, potential candidates for RLT will also include patients with newly diagnosed G2/G3 GEP-NETs and Ki-67 ranging between 10 and 55%" [39].

Would You Consider Using RLT as First-Line Treatment in Patients with G2 SSTR-Positive GEP-NETs?

RLT could be the preferable option in GEP-NET G2 patients considering the weight of QoL and response probabilities.

Specification is needed before answering whether to use RLT as first-line treatment when dealing with pancreatic or small intestine primary tumors. However, results of ongoing randomized clinical trials are expected to give suggestions in this context. Furthermore, dosimetry data shows that pancreatic tumors respond first (i.e., the dose absorption is higher than intestinal tumors) probably because their larger vascularization enables an increased radioligand uptake, which could explain the gap in response rate.

In summary, when tumor shrinkage is the goal, first-line RLT could be used in patients with advanced G2 SSTR-positive GEP-NETs with high uptake, as these tumors are probably more responsive to RLT. However, in patients who are highly symptomatic or patients with rapid tumor growth, chemotherapy should be the preferred option.

How Does the Clinical/Therapeutic Approach Change in Patients with G3 SSTR-Positive GEP-NETs and Ki-67 ≤ 55%?

NETTER-2 data strongly supports the evidence that RLT should be considered a potential first-line treatment in G3 SSTR-positive GEP-NETs compared with high-dose SSA. However, G3

GEP-NETs represent a non-homogeneous clinical entity; therefore, patient selection bias cannot be excluded in NETTER-2. This further underlines the importance of contextualizing the available evidence in the specific clinical case.

Although the control arm of NETTER-2 could seem suboptimal for the G3 GEP-NET setting, several members of the scientific board agreed that finding an alternative solution that would cover both G2 and G3 settings with the same level of evidence would be difficult.

The 2024 ITANET/AIMN/SIE/AIOM position paper recommends that "As soon as RLT is approved by regulatory authorities, it should be considered a valid option for patients with G2-G3 GEP-NETs expressing SSTR (1b–A)" [39]. However, as noted above, approval for first-line use has been granted only in the USA [54], and expanded indications for the use of RLT have not progressed in the European Union [55].

What Clinical Profiles and Characteristics of Patients Affected by G3 SSTR-Positive GEP-NETs with Ki-67 ≤ 55% Would You NOT Suggest RLT as First-Line Treatment?

Real-world evidence suggests that patients who need a rapid and extensive tumor response may be more suitable for chemotherapy, especially in pan-NETs, but this is far from being absolute. Logistics may also favor chemotherapy for patients who struggle to access RLT treatment centers [56].

The level of Ki-67 (21–55%) and FDG functional expression do not seem to influence the therapeutic choice in favor of RLT or chemotherapy. However, it is known that FDG-PET results could have a prognostic value. FDG analysis should be performed to exclude a mismatch SSTR neg./FDG pos., which could be a factor in not proposing RLT. FDG-PET could have a role in helping to better characterize the tumor as a whole and allow for closer monitoring of tumor response. Combined [^{18}F]F-FDG/[^{68}Ga]Ga-DOTA-SSA is proposed to guide treatment strategies in patients with NET [57]. SSTR-PET/CT should be given the most importance as it is the only selection factor for therapy in GEP-NETs. FDG-PET was not mandatory in NETTER-2.

Limited data supports chemotherapy in Si-NETs, and patients with high Ki-67 should preferably be enrolled in clinical trials.

Are There Patient Profiles for Whom You Believe Chemotherapy is More Suitable as First-Line Treatment?

Patient profiles who could benefit from chemotherapy as first-line treatment rather than RLT include patients who are highly symptomatic with rapidly growing tumors (especially in pan-NETs) [35, 39]. The primary tumor site may influence the choice of therapy (i.e., pancreatic ≫ small intestine ≫ stomach). These are the same indications conventionally adopted for RLT.

Is There Potential for RLT in a Perioperative Setting?

RLT could be considered in a preoperative setting in G2 SSTR-positive pan-NETs when tumor shrinkage is a clinical objective, particularly in borderline resectable or oligometastatic or poor prognosis pan-NETs. Therefore, RLT could have potential in patients with borderline resectable disease and in patients with oligometastatic disease where a future radical surgery cannot be excluded in case of good response. This is often discussed in first-line treatment. The evidence that tumor shrinkage occurs by RLT supports this direction [8].

Which Role Does FDG-PET Play in Identifying and Treating Patients Affected by (i) G2 GEP-NETs with Ki-67 ≥ 10% and (ii) SSTR-Positive GEP-NETs with Ki-67 10–20% vs. 20–55%?

The results of FDG-PET are ancillary in decision-making for managing patients with GEP-NETs. They may be used to evaluate a discordance among the total number of disease sites and those expressing SSTRs. Two crucial steps are (1) concordance/discordance between CT/MRI and SSTR-PET/CT and (2) match/mismatch between SSTR-PET/CT and FDG-PET/CT. Thus, the therapeutic strategy, including or not RLT, is usually

made by integrating imaging results, clinical signs/symptoms, hematological and biochemical parameters, life expectancy, and QoL. FDG-PET plays a pivotal role as a prognostic marker.

The 2024 ITANET/AIMN/SIE/AIOM position paper also recommends [^{18}F]FDG PET/CT before RLT in cases with heterogeneous uptake at SSTR-PET and in patients with suspicion of rapidly progressive disease (3b–A) [39].

Which Characteristics of the Morphological and/or Functional Drivers of Tumor Lesions Could Be Used to Guide the Therapeutic Choice?

The most reliable selection criterion is SSTR2 expression/SSTR2 density at tumor sites. SSTR expression is also predictive of response (i.e., correlates specifically with response to RLT) [58], so it must be carefully evaluated. In addition, a hypothetical necrosis visualized on a CT scan and appearing by PET/CT as a photopenic area can be an aid but cannot be decisive unless verified histologically. The size of a tumor lesion(s) may be a factor in aiding therapeutic choice [37].

Two key elements are receptor expression determined by ^{68}Ga PET scan or SSTR receptor scintigraphy (when practical, economical, and regulatory factors limit the use of ^{68}Ga for SSTR imaging [59]). PET/CT imaging can be used to demonstrate SSTR expression prior to treatment, and a prognostic role for functional imaging using [^{68}Ga]Ga-DOTA-SSA PET/CT is described in G3 NETs, which may aid their management [60]. A systematic review and meta-analysis of 2266 patients with NETs from 24 studies found that, alongside its diagnostic abilities, pretreatment staging with [^{68}Ga]Ga-DOTA-SSA PET/CT modified clinical management in a third of patients and may predict RLT response [61].

Three Key Points Regarding RLT Must Be Addressed

(i) Is [^{68}Ga]Ga-PET/CT-DOTA-SSA a systematic routine tool that should be performed in all GEP-NETs, and when should it be performed? We suggest performing it: (a) within the 4 weeks before starting RLT, (b) at least 8–12 weeks after the end of RLT treatment (4 doses), and (c) when signs and symptoms suggest clinical progression. [^{68}Ga]Ga-PET/CT-DOTA-SSA should always be performed at baseline, i.e., at diagnosis.

(ii) Which patients are eligible for RLT, and how is feasibility defined? The best candidate is represented by a patient with NET progression, having a positive SSTR imaging (Krenning score ≥ 2), stressing that PET/CT with [^{68}Ga]Ga-DOTA-SSA is the most accurate imaging modality, and a complete clinical evaluation to avoid a useless treatment in compromised patients.

(iii) What should be the time to start RLT administration? Nowadays, RLT is indicated when NET will progress after SSAs. Morphological and functional imaging should be carefully considered and applied when symptoms and signs will change, or there is a strong suspicion of disease progression. There are no rules for fixed intervals.

These key points are crucial because not all patients with SSTR-PET-positive GEP-NETs receive RLT or will receive it at a standard timing.

Can the NETTER-2 Data Fill the Gaps Faced in Clinical Practice and Lead to a Change in Patient Evaluation and Therapeutic Approach?

The scientific board agreed that RLT should always be considered in GEP-NETs, including low-grade tumors. High-dose SSA should not be considered a therapeutic option if a non-functioning patient with NET is a candidate for RLT. Moreover, high-dose SSA is not approved for non-functioning GEP-NETs. Furthermore, the findings from the NETTER-2 trial confirm that selecting appropriate therapy for patients with GEP-NETs should be guided primarily by clinical symptoms, the presence of a functional syndrome, and the density of SSTR expression within tumor site(s). This approach contrasts with traditional methods that rely mainly on tumor histology and grading, which form the

foundation of current treatment guidelines. To support clinical decision-making, there is a pressing need for a clear, concise, and practical algorithm that clinicians can apply in everyday practice. However, significant variability and, in some cases, outdated recommendations among existing international guidelines make it difficult to establish a uniform approach for developing such an algorithm. As a result, current guidance falls short in enabling the consistent personalization of therapy for the diverse group of patients with GEP-NETs.

The development of a robust and practical algorithm must therefore await the publication of updated guidelines. These should incorporate emerging high-level evidence, such as that provided by the NETTER-2 trial, to better define the role of RLT and other therapies in the management of GEP-NETs and to ensure that treatment recommendations keep pace with advances in the field.

Clinical progression must be based on evidence. However, it can be summarized as "the presence of symptoms or signs on a patient." For example, the increase of standardized uptake values (SUV) in a ^{68} Ga-PET scan should not be viewed as an element of progression [41]. A change in treatment regimen is acceptable in the presence of clinical progression if it is based on an observed clinical change (i.e., a symptomatic clinical progression or signs on the patient) and not on biochemical signs only (i.e., CgA rise). It should also be considered that the clinical interpretation of the term "progression" to SSA currently represents a limit to propose RLT as a result of regulatory rules as it is not objective nor well defined but is arbitrary and based on various aspects. The NETTER-2 results provide a solid basis for earlier utilization of RLT, which will require extending the indication in the European Union to align with the USA.

CONCLUSIONS

The decision to use RLT to treat GEP-NETs should be based on several factors, including the SSTR tumor expression and the patient's clinical needs. Patients should be managed within a multidisciplinary team, and the importance of a discussion within a tumor board should not be overlooked. However, well-defined practical guideline recommendations related to RLT are lacking, and its optimal positioning in treatment algorithms is debated.

The NETTER-2 trial demonstrated the efficacy and safety of RLT, specifically [^{177}Lu] Lu-DOTA-TATE, as first-line treatment in patients with newly diagnosed, well-differentiated, advanced G2 and G3 GEP-NETs. A pronounced impact in terms of ORR and survival outcomes was reported in pNETs. At present, it is extremely challenging to evaluate the prospects of change in clinical practice using the NETTER-2 approach. Whether NETTER-2 outcomes can bridge the gaps encountered in real life (clinical practice) and lead to a change in patient evaluation and therapy is yet to be elucidated, which can be expected as treatment guidelines are updated.

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