Cancer Treatment Reviews 117 (2023) 102560

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevier.com/locate/ctrv

Anti-tumour Treatment

Targeting neuroendocrine tumors with octreotide and lanreotide: Key points for clinical practice from NET specialists

A. La Salvia [a], R. Modica [b], R.E. Rossi [c], F. Spada [d], M. Rinzivillo [e], F. Panzuto [e,f], A. Faggiano [g], S. Cinieri [h,1], N. Fazio [d,*]

[a] National Center for Drug Research and Evaluation, National Institute of Health (ISS), Rome, Italy
[b] Department of Clinical Medicine and Surgery, Endocrinology Unit of Federico II University of Naples, Naples, Italy
[c] Gastroenterology and Endoscopy Unit, IRCCS Humanitas Research Hospital, Via Manzoni 56, Rozzano, Milan, Italy
[d] Division of Gastrointestinal Medical Oncology and Neuroendocrine Tumors, IEO, European Institute of Oncology, IRCCS, Milan, Italy
[e] ENETS Center of Excellence, Digestive Disease Unit, Sant'Andrea University Hospital, Rome, Italy
[f] Department of Medical-Surgical Sciences and Translational Medicine, Sapienza University of Rome, Rome, Italy
[g] Department of Clinical and Molecular Medicine, Sant'Andrea Hospital, ENETS Center of Excellence, Sapienza University of Rome, Rome, Italy
[h] Medical Oncology Division and Breast Unit, ASL Brindisi, Brindisi, Italy

ARTICLE INFO

Keywords:
Long-acting somatostatin analogs (SSA)
Neuroendocrine tumors (NET)
Efficacy
Safety
Feasibility

ABSTRACT

Octreotide and lanreotide are the two somatostatin analogs (SSA) currently available in clinical practice. They have been approved first to control the clinical syndrome (mainly carcinoid syndrome) associated with functioning neuroendocrine tumors (NET) and later for tumor growth control in advanced low/intermediate grade NET. Although evidence regarding their role, especially as antiproliferative therapy, has been increasing over the years some clinical indications remain controversial. Solicited by AIOM (Italian Association of Medical Oncology) a group of clinicians from various specialties, including medical oncology, endocrinology, and gastroenterology, deeply involved in NET for their clinical and research activity, addressed eight open questions, critically reviewing evidence and guidelines and sharing clinical take-home messages. The questions regarded the use of long-acting octreotide and lanreotide in the following settings: functioning and non-functioning NET refractory to label dose, first-line metastatic pulmonary NET, combination with other therapy with an antiproliferative intent, maintenance in NET responding to other therapies, adjuvant treatment, Ki-67-related cut-off, somatostatin receptor imaging, safety, and feasibility. The level of evidence is not absolute for the majority of these clinical contexts, so it is recommended to distinguish routine versus sporadic utilization in very selected cases. Mention of such specific issues by the main European guidelines (ENETS, European Neuroendocrine Tumor Society, and ESMO, European Society for Medical Oncology) was explored and their position reported. However, different clinical decisions on single patients could be made if the case is carefully discussed within a NET-dedicated multidisciplinary team.

Introduction

Epidemiological notes

Neuroendocrine neoplasms (NEN) are a variegated family of malignancies originating from the diffuse neuroendocrine system. They are mainly distinguished into "well differentiated" (WD) and "poorly differentiated" (PD) and are commonly named neuroendocrine tumors (NET) and neuroendocrine carcinomas (NEC), respectively. This derives from the gastroenteropancreatic (GEP) WHO classification terminology that categorized these neoplasms in WD NET grades 1, 2 and 3 or PD NEC [1]. Specifically, a Ki-67 $>$ 20% defines the high-grade category,

* Corresponding author at: Division of Gastrointestinal Medical Oncology and Neuroendocrine Tumors, European Institute of Oncology, IEO, IRCCS, Via Ripamonti 435, 20141, Milan, Italy.
E-mail addresses: anna.lasalvia@iss.it (A. La Salvia), roberta.modica@unina.it (R. Modica), robertaelisa.rossi@gmail.com (R.E. Rossi), francesca.spada@ieo.it (F. Spada), mrinzivillo@ospedalesantandrea.it (M. Rinzivillo), francesco.panzuto@uniroma1.it (F. Panzuto), antongiulio.faggiano@uniroma1.it (A. Faggiano), saverio.cinieri@me.com (S. Cinieri), nicola.fazio@ieo.it (N. Fazio).
[1] AIOM National President.

https://doi.org/10.1016/j.ctrv.2023.102560
Received 13 February 2023; Received in revised form 8 April 2023; Accepted 12 April 2023
Available online 17 April 2023

including NET G3 and NEC [2]. Pulmonary carcinoids with high Ki-67 are quite rare [3], and they were mentioned in the latest edition of the lung/thymus NEN WHO classification as NET with high mitotic count and/or Ki-67 > 30% [1].

The vast majority of NET originate in the GEP tract (approximately 60%) followed by the lung (approximately 30%), although they may develop in many anatomic sites [4,5]. The incidence of NET has substantially increased over the last decades, reaching 6.98 new cases/100,000/year [6,7]. Their prevalence is high due to their relatively indolent nature [6].

The prognosis of these neoplasms is extremely various mainly according to some key features, such as tumor differentiation, proliferation index, primary site and TNM stage [6].

In most cases, NET express somatostatin receptors (SSTRs) on cell surface, particularly the subtype 2 and 5 ($SSTR_2$ and $SSTR_5$). This aspect is essential for the diagnostic characterization (with functional imaging e.g. 68Ga-based PET/CT) and prediction to treatment (particularly to peptide receptor radionuclide therapy, PRRT), that come within the concept of "Theragnostics" [8].

Octreotide and lanreotide are the only two somatostatin analogs (SSA) currently utilized in clinical practice. Therefore, the term "SSA" will be utilized through the text to mean "octreotide and lanreotide".

Biology

Octreotide and lanreotide are synthetic octapeptides, with a longer half-life than native somatostatin 14 and 28, which are the two somatostatin (SST) physiologically functional subforms [9]. This aspect is crucial for clinical use. Somatostatin signalling is important for cell cycle regulation, inducing apoptosis, inhibition of growth factor effects and decreased hormone secretion [10]. The activity of SST is mediated by its binding to five subtypes of SSTRs [11]. Octreotide and lanreotide share a similar SSTR binding profile, with high $SSTR_2$ affinity, moderate $SSTR_5$ affinity, some affinity for $SSTR_3$, but none for $SSTR_1$ and $_4$ [12]. SSTR are expressed in various normal and neoplastic tissues (such as melanoma, prostate, breast, ovary, thyroid, and gastrointestinal cancers) [13]. Among these, the expression in NET (above all of $SSTR_2$ and $SSTR_5$) is the most relevant for both diagnostic and therapeutic implications [14].

Octreotide and lanreotide have demonstrated firstly to provide a control over hormonal cell secretion and then they have shown also an anti-proliferative effect [15,16]. Somatostatin analogs have been reported to have two potential mechanisms of action, one receptor-mediated and the other not mediated by the receptor, including the inhibition of the release of growth factors and trophic hormones (such as IGF-1 and insulin), the inhibition of angiogenesis, and the modulation of the immune system [17].

Pharmacology (Pharmacodynamic and Pharmacokinetic Properties)

Octreotide and lanreotide are extremely more potent and selective if compared to SST. Moreover, these agents exhibit greatly-extended half-lives (of 1–2 h compared with the 1–3 min of SST). The development of depot formulation of octreotide and lanreotide further improved the clinical application of these compounds. Therefore, SSA are characterized by a much lower clearance and improved metabolic stability in the circulation and in target organs, with longer lasting therapeutically relevant plasma and tissue levels and therefore in a longer duration of action [18]. Both octreotide and lanreotide are commercially available and approved for the treatment of functioning and non-functioning NET.

Octreotide

Octreotide long acting repeatable (LAR) is available at doses of 10 mg, 20 mg and 30 mg. Octreotide LAR has a relative bioavailability of 60% compared with subcutaneous octreotide [19]. The initial recommended dose for the treatment of NET is 30 mg every 4 weeks with intramuscular injection [20]. The reconstitution procedure requires refrigerated storage and encompasses seven different preparation steps, including handling to ensure homogenous suspension of the product. Octreotide selectively binds to $SSTR_2$ (median inhibitory concentration [IC50] 0.6 nmol/L) and to a lesser extent SST_5 (IC50 7 nmol/L). Octreotide LAR retains the pharmacological characteristics of subcutaneous octreotide and reaches steady-state concentrations within three injections. The short-acting formulation is rarely used for long-term therapy, but can be particularly useful to optimize the control of hormonal secretion in selected cases (e.g. in the prevention of carcinoid crisis in patients with carcinoid syndrome undergoing invasive procedures) [21].

Lanreotide

Lanreotide autogel (ATG) is available at doses of 60 mg, 90 mg, or 120 mg [22]. The initial recommended dose for the treatment of NET is 120 mg administered every 4 weeks by deep subcutaneous injection allowing to reach steady-state concentrations after 4–5 injections. Lanreotide binds with high affinity to $SSTR_2$ (IC50 0.8 nmol/L) and with a lesser affinity to $SSTR_5$ (IC50 5.2 nmol/L) [23]. It is widely metabolized in the gastrointestinal tract and excreted through the biliary tract, with a half-life of 23–30 days. The absorption of lanreotide ATG is rapid after administration of a single dose, with a linear dose-proportional profile for maximum serum concentration (Cmax) and the area under the concentration–time curve (AUCs) during an administration interval values [24].

Aims

This narrative review is aimed to critically analyse the efficacy, safety and feasibility evidence data of long-acting octreotide and lanreotide therapy in patients with advanced GEP or pulmonary NET, particularly focusing on some controversial applications of clinical practice.

Discussion and expert opinion

1. *Is a positive SSTR-related functional imaging necessary to use an SSA as an antiproliferative agent in daily clinical practice?*

   The ENETS Consensus Guidelines for the standard of care in NET stated that SSTR status should be positive on somatostatin receptor imaging (SRI) only if an SSA is going to be used with antiproliferative intent [25]. The underlying implication that SSA can be used with antisecretory intent irrespective of the SSTR status is supported by robust evidence of clinical response to SSA in patients with NET-related endocrine syndromes. SSTR expression is considered a key feature of GEP-NENs in ESMO guidelines, where the therapeutic approach is modulated according to SSTR positivity. In NET with negative or weakly positive SSTR, SSA are not included in the therapeutic algorithm [26]. Nevertheless, SSA can be tried in SSTR-negative NET, in case of low tumour burden or small lesion due to potentially false-negative SSTR status. Positive SSTR status is generally required although not predictive of response [26]. According to AIOM guidelines, the expression of SSTR is mandatory for the use of antiproliferative therapy with SSA.

   In PROMID trial, octreotide LAR 30 mg/monthly was administered regardless of SSTR status in both functioning and non-functioning NET with proof of a WD histology [27]. In this study, the SRI with octreoscan® was positive in 32 (of 42) patients treated with octreotide LAR and in 31 (of 43) patients in the placebo arm. On the contrary, SSTR positivity was an inclusion criterion in CLARINET trial, where lesions had to be classified on SSTR scintigraphy as Krenning grade $\geq$ 2 to be treated with lanreotide ATG 120 mg every 28 days [28]. Both trials demonstrated the antiproliferative activity of long-acting octreotide and lanreotide respectively, but differences

according to SSTR positivity were not available. SSTR imaging was not included in RADIANT-2 trial comparing 10 mg daily everolimus with placebo, both in conjunction with octreotide LAR 30 mg every 28 days [29], while functional SSTR expression on all target lesions confirmed by blinded, independent central review was required for enrolment in NETTER-1, comparing ^{177}Lu-DOTATATE 7.4 GBq every 8 weeks (four intravenous infusions, plus best supportive care including octreotide LAR administered intramuscularly at a dose of 30 mg) with octreotide LAR alone 60 mg every 4 weeks [30]. Noteworthy, in clinical trials not requiring SSTR-related functional imaging before enrolment, low-grade or intermediate-grade histology was mandatory.

An SSA is generally recommended as a first-line treatment option to slow down disease progression in patients with advanced NET with SSTR imaging positivity. Importantly, when defining a NET as negative or with indeterminate SSTR imaging, it is highlighted that the type of imaging test may influence results, since ^{68}Ga-DOTA-TOC/NOC/TATE-PET/CT (SSTR-PET) imaging has considerably improved diagnostic accuracy compared with labeled somatostatin scintigraphy. Furthermore G1/2 NETs with true SSTR expression negative by functional imaging are rare, and this explains why a histology of low-grade NET supports a therapy with SSA.

The efficacy of SSA for tumor control in SSTR-negative pancreatic NET (panNET) is considered less clear, but in indolent, low-volume SSTR-negative panNET their use can be suggested due to the relatively benign side-effect profile, although the likelihood of efficacy is considered low [31].

Summary

According to the current evidence a positive SRI is not necessary in absolute, although recommended, to start an antiproliferative SSA therapy in daily clinical practice, provided a favorable clinical context, including an indolent tumor, limited tumor burden and asymptomatic patient. In rare clinical situations the SRI could be negative due to technical reasons, such as the very low size of the lesions. However, we suggest that each single case of negative SRI where it is supposed to use an SSA should be discussed within a NET-dedicated multidisciplinary team. The non-receptor-mediated effect of SSA should be considered as well.

2. *Is there a threshold of Ki-67 to be respected to use an SSA as an antiproliferative treatment in NET in daily clinical practice?*

Long-acting lanreotide and octreotide are commonly utilized in daily clinical practice in many countries in patients with advanced WD GEP and pulmonary NET, based on their approval by European Medical Agency (EMA) and Food and Drug Administration (FDA) as an anti-tumor therapy. There is not a specific reference to the Ki-67 value in the approval, similarly to some guidelines, like ENETS and AIOM/ITANET (https://www.aiom.it, 2022), although a clear recommendation limited to GEP NET with $< 10\%$ Ki-67 is reported in the latest edition of the ESMO guidelines.

However, evidence is stronger for lower Ki-67 values. In the two major clinical trials of antiproliferative use of these drugs in GEP NET, the randomized phase III PROMID [27] and CLARINET [28], the Ki-67 was within a precise threshold. In the PROMID study [27] the Ki-67 was $\leq$ 2% in the 97.6% of midgut NET treated with octreotide LAR, whereas in the CLARINET trial [28] the Ki-67 was 0–2% in 68% and 3–10% in 32% of non functioning enteropancreatic NET receiving lanreotide ATG.

On the other hand, a retrospective real-world analysis of 43 patients with advanced SSTR-positive panNET, included various Ki-67 values. Patients were treated with octreotide LAR as first-line therapy showing a more durable response when they had a NET with a Ki-67 $\leq 10\%$ compared to those with a Ki-67 $> 10\%$ [32].

Regarding pulmonary NET, in the only phase 3 trial, the SPINET [33], a precise cut-off of Ki-67 was not required, and no conclusions can be drawn in this regard. Two retrospective studies [34,35] reported a significant longer survival rates for pulmonary NET patients treated with SSA, with $\leq 5\%$ versus $> 5\%$ Ki-67.

A 5% Ki-67 threshold was identified as significant for PFS in a multicentre Italian observational study conducted on 140 G1-G2 GEP and pulmonary NET receiving long-acting SSA [36].

Also in the phase 3 AXINET trial a better antitumor effect was observed for extrapancreatic NET with Ki-67 $\leq 5\%$ compared with $>$ 5% [37] Ki-67.

Real-world studies (carried out in Italy [38], France [39] and UK [40], reported that $>$ 30% of NET G3 were treated with SSA, although tumor response rate was not so encouraging.

Summary

In WD GEP or low-grade pulmonary NET, regulatory authorities and some guidelines did not strictly limit SSA to a specific Ki-67 threshold, so theoretically they could be considered even in WD NET with higher Ki-67 values. However, it should be noted that the current evidence is more robust on NET with $\leq 10\%$ Ki-67, particularly $\leq 5\%$. Therefore, their use should be focused on that setting, although it cannot be excluded that in selected cases of patients with $>$ 10% Ki-67 GEP or pulmonary NET a long-acting SSA can be effective These latter cases should be preferably discussed in a NET-dedicated context by considering characteristics of both tumor and patient and therapeutic alternatives.

3. *Is there enough evidence to use an SSA as an adjuvant therapy in NET in daily clinical practice?*

In NET, the role of adjuvant therapy has not been specifically investigated with any type of therapy including SSA. For this reason, the literature cannot represent a support for the use of SSA with the aim of preventing recurrences in patients with radically resected localized or locally advanced NET.

The main European guidelines (ENETS, ESMO) agree in underlining how, after curative surgery, there is no indication to use an adjuvant SSA, in patients with radically resected GEP or pulmonary NET (NEN Guidelines, AIOM/ITANET, https://www.aiom.it, 2022) [26,41].

The AIOM/ITANET guidelines recommended that “in patients with GEP-NET, non-functioning, undergone radical surgical resection, a treatment with SSA should not be considered” with an adverse grade of recommendation. In Italy, outside clinical trials, an SSA is autorized to be prescribed only in patients with non-functioning metastatic or unresectable locally advanced NET or for controlling the NET-related clinical hormonal syndrome in “functioning tumors”.

Therefore, an adjuvant SSA is not currently indicated in patients with completely resected NET [42]. This was also suggested by a recent multicenter study [43], including 137 radically resected NET patients who received an adjuvant therapy with chemotherapy and/or SSA; both therapies were negatively associated with recurrence free survival and conferred no overall survival (OS) benefit in resected stage I-III patients.

Summary

The use of SSA as an adjuvant therapy in patients with a radically resected GEP or pulmonary NET should not be considered in daily clinical practice as there is no specific evidence to support this. AIOM/ITANET, ENETS and ESMO guidelines agree not to indicate an SSA to this aim.

4. *Is there enough evidence to utilize an SSA as maintenance therapy and/or in combination with other anti-tumor therapies in non-functioning NET patients in daily clinical practice?*

The role of SSA for maintaining tumor growth control after initial upfront treatment has also been recently investigated. This issue was not addressed in ENETS and AIOM/ITANET guidelines, whereas it is briefly reported in the supplementary material, section 6, of the ESMO guidelines [44], where it is detailed only that it is unclear if

SSA should be continued after PRRT as a maintenance therapy. The available data about the maintenance strategy are conflicting [45], above all regarding the utility of SSA as maintenance therapy after PRRT. In this context, a few retrospective analyses reported a clear survival benefit by using maintenance SSA [46,47]. Conversely, in a recent prospective study, no advantage in terms of PFS and OS by using octreotide LAR vs best supportive care as maintenance therapy after initial response to PRRT was showed [48].

Combining SSA with other treatments approved for advanced NET (PRRT, everolimus or sunitinib, and chemotherapy) is considered a potentially effective and safe approach in daily clinical practice, owing to the favorable safety profile of these drugs, and the potential synergistic activity between SSA and the other treatments [49]. Octreotide LAR 30 mg q4w was combined with ^{177}Lu-DOTATATE in the successful phase 3 trial, NETTER-1, that reported a markedly longer PFS and OS in advanced midgut NET treated with PRRT plus SSA as compared to those who underwent high-dose octreotide LAR alone [30]. Although this study was positive it cannot answer the question if an SSA should be added to PRRT in non-functioning small-bowel NET as it was not designed to this scope and it included both functioning and non-functioning NET.

The combination of SSA with everolimus showed a promising survival advantage in pre-treated advanced panNET patients in the phase II non-randomised RADIANT-1 study [50], as well as as first-line therapy in GEP or pulmonary NET patients included in the phase II single-arm ITMO study [51]. These data were confirmed at the 5-year update [52].

A recent network *meta*-analysis, including eight randomized controlled studies [53], supported the use of the combination of SSA plus everolimus in non-functioning NET. However, these findings should be cautiously interpreted considered the heterogeneity of the included studies, the lack of long-term follow-up, the paucity of data regarding treatment-related adverse events.

As far as combination treatment with temozolomide (TMZ) no randomised trials exist. Two phase II single-arm prospective studies investigated the upfront combination of lanreotide ATG plus TMZ in patients with advanced progressive functioning or non-functioning GEP-NET [54] and lung/thymic NET [55].

Summary

Implementation of maintenance SSA after tumor response to an initial upfront therapy is a safe approach, which may provide potential clinical benefit without adding significant toxicity, however the level of evidence is quite poor regarding this topic. In addition, based on the current evidence, SSA use as antiproliferative therapy in combination with other anti-tumor therapies, such as PRRT, targeted agents or chemotherapy (in particular TMZ), in patients with advanced non-functioning GEP or pulmonary NET is not justified as a routine use. However, both the maintenance and combination strategy could be considered for very selected cases carefully discussed within a NET-dedicated multidisciplinary team clearly reporting the rationale and the potential clinical advantages of this strategy.

5. *Is there enough evidence to use an SSA as antiproliferative therapy in metastatic pulmonary NET in daily clinical practice?*

Advanced pulmonary NET with low proliferation index and positive SRI are usually treated with SSA as first-line treatment. According to AIOM/ITANET (https://www.aiom.it, 2022), ESMO and ENETS guidelines, SSA are recommended first-line in typical carcinoid or slowly progressing advanced SRI-positive pulmonary NET [56,57]. However, the efficacy of SSA has been proven in phase III clinical trials in metastatic GEP-NET, but not in pulmonary NET. On the other hand, the molecular basis for SSA treatment is a high and specific SSTR2-5 expression, which has been demonstrated in pulmonary as well as in GEP NET [58]. Indeed, many clinical experiences demonstrate the activity and safety of SSA for pulmonary NET patients [59,60].

Long PFS and OS were obtained with SSA as first-line approach in 31 consecutive progressive, metastatic pulmonary NET from two Italian referral centres [35]. Functioning and slowly progressive pulmonary NET seem to have a better prognosis compared to non-functioning and highly progressive NET when treated with SSA, according to a retrospective French study [61].

The phase II single-arm ATLANT trial prospectively evaluated the efficacy and safety of lanreotide 120 mg in combination with temozolomide in unresectable advanced thoracic NET with encouraging results, though the primary endpoint (9-m DCR) was not statistically met [55].

In a subgroup analysis of the RADIANT-2 trial in patients with advanced pulmonary NET, the association of everolimus and octreotide LAR improved mPFS by 2.4-fold compared with placebo plus octreotide LAR, consistently with the overall trial results [62].

A phase III, prospective, multicenter, randomized, double-blind, SPINET trial aimed to compare the efficacy and safety of lanreotide 120 mg q4w plus Best Supportive Care (BSC) versus placebo plus BSC for advanced, typical or atypical pulmonary NETs [33]. The power of the study was impaired due to the premature stop due to the slow accrual and inclusion of SSA in guidelines (2015/2016), so all enrolled patients went to the open label treatment and follow-up phases. Remarkably a quite long PFS of 16.6 months was observed in all patients receiving lanreotide ATG.

Summary

As for pulmonary NET, although the body as well as the level of clinical evidence is lower than that of GEP NET and there is not a conclusive phase III trial unlike GEP NET, the use of a first line SSA as antiproliferative therapy, preferably in low-grade NET with positive SRI, is justified.

6. *Is there enough evidence about efficacy and safety to use above-label dose of octreotide or lanreotide in non-functioning advanced NET progressing on label dose SSA in daily clinical practice?*

It is common experience that non-functioning NET may progress on label dose SSA and the use of unconventional dose in such cases has been applied in daily clinical practice, although specific studies are scanty and with controversial results and the choice to modify the label dose is often based on personal attitude [63]. This topic is not clearly addressed in the national and international guidelines. ENETS guidelines, reported that this option could be considered in a hypothetic sequence of therapies in patients with non-functioning advanced NET of the midgut progressive on previous *watch and wait* strategy or treatment with label dose of SSA or further line of therapy. (NEN Guidelines, AIOM/ITANET, https://www.aiom.it, 2022) [25,26].

In the CLARINET FORTE, a prospective non-randomized phase-2 trial [64], 99 patients with metastatic or locally-advanced, grade 1 or 2 midgut or pancreatic, functioning or non-functioning NET were treated with LAN 120 mg q2w for up to 96 weeks (midgut cohort) or 48 weeks (pancreatic cohort). Reducing the dosing interval to q2w provided encouraging PFS, particularly in patients with a Ki-67 $\leq$ 10%; of note, no deterioration in quality of life was observed. As regards safety, this study reported a 1% proportion of patients experiencing severe treatment-related adverse events when receiving above label-dose of lanreotide, and a minimal risk of withdrawals due to drug-related adverse events.

A systematic review [65], including 18 studies for a total of 1002 patients with histologically confirmed NET, reported that escalated-dose SSA was well tolerated in patients with GEP-NET, with significant rates of disease control.

In a recent multicenter Italian study involving 13 NET-dedicated centers [66], a total of 140 patients with WD G1 or G2 GEP-NET (of whom 93 with non-functioning tumors) were treated with unconventional dose of SSA (achieved by both increasing dose intensity

to every 14–21 days or dose density, i.e. lanreotide 180 mg or octreotide LAR 60 mg every 28 days). According to this study, the administration of high-dose SSA was associated with a longer PFS, particularly if early administered as second-line therapy. However, often high-dose SSA are recommended as a second-line treatment for patients with very slowly progressive tumors. Therefore, the comparison to other treatments, above all according to retrospective analyses, could be misleading. With this regard, less encouraging results have been reported by a recent *meta*-analysis [67], reporting that unconventional SSA dose should not be the preferred antiproliferative treatment choice in patients with GEP NET who progressed on label dose SSA because of the short PFS, and low disease control rate.

A survey on SSA use conducted in Italy among the AIOM members, in 2014, showed that in nonfunctioning NEN progressing on label dose SSA around half of respondents had increased the dose of octreotide LAR or lanreotide depot above the upper label dose, mainly shortening the administration interval [68].

Focusing specifically on safety, the AIOM/ITANET as well as the ESMO/ENETS guidelines did not address specifically this topic. However, data coming from clinical trials (as the NETTER-1 trial, where no significant toxicity was reported in the control group, receiving above label dose octreotide LAR 60 mg q4w [30]) show a similar safety profile as to that reported by studies investigating label dose SSA, confirming that increasing the SSA dose above the label one is safe.

Summary

According to the current evidence, treatment with above-label dose SSA in non-functioning advanced NET progressing on label dose SSA is a safe and well-tolerated option. However, a clear benefit in terms of tumor growth control has not been observed. Therefore, this therapeutic option should not be routinely considered in daily clinical practice, although it could be discussed within NET-dedicated multidisciplinary teams in very selected cases of very indolent progressive disease of asymptomatic patients and always compared with alternative therapeutic options.

7. *Is there enough evidence about efficacy and safety to use above-label dose of octreotide or lanreotide in functioning NET progressing on label dose SSA in daily clinical practice?*

In clinical practice the use of above-label dose SSA, can be obtained by increasing the dose of the single administration and/or increasing the frequency of administrations. This is commonly applied in patients with functioning NET progressing on label dose SSA. Despite the limitations of the real-world evidence the above-label dose use of octreotide and lanreotide was included in some guidelines ([25,26], NEN Guidelines, AIOM/ITANET, https://www.aiom.it, 2022). For instance, ESMO reported that "above labelled dosages [shortening of the injection interval of long-acting SSAs (lanreotide 120 mg; octreotide 30 mg) to every 3 or 2 weeks instead of every 4 weeks] (off-label) or short-acting octreotide s.c. as additional injections" can be done in case of uncontrolled carcinoid syndrome."

The beneficial effect of label dose SSA in controlling hormonal hypersecretion in functioning NET may decrease over time, maybe due to down-regulation/internalization of SSTR, as well as the outgrowth of clones lacking the expression of SSTR due to prolonged exposure [69] and increasing SSA dose was already successfully used in GH-secreting pituitary NET [70].

Data derived from retrospective studies investigated the switch to above-label dose SSA in patients with clinically uncontrolled functioning NET mainly induced a complete/partial control of endocrine symptoms in 30/70% of cases, respectively, in 28 NET patients progressive on label dose SSA [71].

In a retrospective study of 30 GEP NET patients, a proportion of patients with an uncontrolled syndrome treated with increased dose of octreotide LAR, showed a trend toward increased time before further treatment, compared to 24 patients receiving label dose octreotide LAR [72]. A clinical benefit, particularly by improving flushing and diarrhea control, in patients with refractory carcinoid syndrome, was observed after dose titration of octreotide LAR in a retrospective analysis of 338 patients with metastatic midgut NET [73]. Similarly, another retrospective study showed a clinical benefit in patients with refractory diarrhea and flushing when they received above-label dose of octreotide LAR; circulating tumor markers did not correlate with symptom relief [74].

A survey on SSA use conducted in Italy among the members of the AIOM in 2014, showed that in functioning NET with clinical syndrome (usually carcinoid syndrome) resistant to label dose SSA, more than half of respondents had used above-label dose of both octreotide LAR and lanreotide depot, mainly shortening the administration interval [68].

Summary

In daily clinical practice the switch to above-label dose SSA seems to be justified when there is a clinical syndrome (especially carcinoid syndrome) refractory to label dose SSA. It can be obtained by increasing the dose of the single administration and/or by shortening the interval between the administrations. Taking into account the available data, the safety profile seems to be similar to that of the label dose SSA.

8. *Is there difference between octreotide and lanreotide in terms of safety and feasibility?*

National (AIOM/ITANET, https://www.aiom.it, 2022) and international guidelines (ESMO and ENETS) do not sustain a preference between one of these two SSA according to the safety profile. The most frequent adverse events occurring with SSA are gastrointestinal symptoms, including abdominal pain and discomfort, diarrhea, and nausea. In addition, approximatively 20% of patients receiving these drugs may develop exocrine pancreatic insufficiency, due to the inhibitory activity of SSA on pancreatic function [75]. Hypo- or hyper-glycemia, development of gallstones and, more rarely, arrhythmia may also occur [76]. However, treatment withdrawal due to adverse events is very rare, particularly with lanreotide. In fact, only 1% of patients in the phase-3 CLARINET study evaluating lanreotide autogel 120 mg q4w versus placebo in WD GEP NET required the treatment discontinuation due to drug-related side effects [28]. Conversely, octreotide LAR was interrupted in 12% of patients enrolled in the PROMID study, evaluating octreotide LAR 30 mg q4w compared to placebo in midgut NET patients [27].

Data from comparative studies aimed at evaluating the specific safety profile of the two SSA, are scanty. A randomized, single-blinded study reported that the proportion of patients experiencing pain in the site of the drug injection was similar between octreotide LAR and lanreotide ATG [77]. Recently, a survey among nurses involved in the drug administration was performed, suggesting a potential advantage for lanreotide compared to octreotide, owing to the specific features (i.e. larger flanges, more rigid needle cap, novel plunger support, new protective tray) of the novel lanreotide syringe [78]. In that study, almost all involved nurses (97.8%) reported a preference for lanreotide compared with octreotide. This finding has been further corroborated by a recent international survey, aimed at investigating the patients' injection experience with the latest available devices of long-acting SSA in patients with NET and acromegaly [79]. In the PRESTO-2 study, a significantly lower proportion of patients experienced pain after injection with lanreotide compared to octreotide (6% vs 22.8%, $p < 0.0001$), and more patients reported interferences with daily activities by using octreotide. Furthermore, patients receiving lanreotide were less likely to experience technical problems during the drug injection when compared to those receiving octreotide.

Finally, a lower risk for treatment discontinuation and a higher

probability to maintain greater treatment duration (31.8 months vs 22.1 months) have been observed with lanreotide compared to octreotide, as reported by a recent real-world observational study [69].

Summary

Both SSA are safe, with excellent tolerability and extremely low risk of serious adverse events. According to available data, a very slight advantage could be recognized for lanreotide in terms of drug administration, interference with the daily activities, and risk of experiencing technical problems during the injection process.

Overall, the questions discussed in this narrative review are reported in Table 1. Their relations with national Italian (AIOM/ITANET) and international ENETS and ESMO guidelines are summarized in Table 2.

Conclusions

Octreotide LAR and lanreotide ATG are widely utilized in clinical practice for patients with NET. The critical analysis of ten clinical-pratical open questions by a NET multispecialist group of clinicians showed that overall, the level of evidence is relatively low for the majority of these key points and, therefore, general recommendations, e.g. in the main guidelines, are quite strict. However, due to the lack of firm limits in the approval labels by the international and local regulatory authorities there is an arbitrary and therefore heterogeneous use of SSA in these settings in the daily clinical practice. In conclusion, we think that the routine use of SSA in clinical settings not covered by a high-level of evidence should be discouraged. On the other hand, therapeutic choices can be personalised for every single patient, as long as carefully discussed within NET-dedicated multidisciplinary teams.

Author contributions

All authors contributed to the development of the publication and maintained control over the final content. The authors did not receive professional help with the preparation of the manuscript. Individual contributions to the paper (according to CRediT roles): Conceptualization, A.L.S., N.F.; writing—original draft and preparation, A.L.S., R.M., R.E.R., F.S., M.R., F.P., A.F., S.C., N.F. writing—review and editing, A.L.S., R.M., R.E.R., F.S., M.R., F.P., A.F., S.C., N.F.; project administration, F.P., A.F., S.C., N.F.; visualization, R.M., R.E.R., F.S., M.R.; English revision, A.L.S., R.M., R.E.R., F.S., M.R.; supervision, A.L.S., N.F. All authors have read and agreed to the published version of the manuscript.

Funding statement

This research received no external funding.

Conflict of interest statement

A.L.S., R.M., R.E.R., M.R., F.P. and S.C. have no conflict of interests to declare. F.S. has received: Grants for Papers writing from Advanced Accelerator Applications (AAA), MSD and Merck, consulting fees from AAA, MSD and Merck, payment for educational activities from AAA, Ipsen, Support for attending meetings and/or travel from I.T.A.N.E.T., F. S. has also participated to LOLA trial meeting Fondazione IRCCS Istituto Nazionale dei Tumori, Milan and at the Safety Monitoring Group HutchMed EU NET, F.S. has a Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid in AIOM full member; ITANET member of scientific committee; ESMO member of Neuroendocrine and Endocrine faculty; A.F. has received consulting fees from AAA, Ipsen, payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from AAA, Ipsen, Support for attending meetings and/or travel from Ipsen, Participation on a Data Safety Monitoring Board or Advisory Board of Ipsen; N.F. Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from AAA, Ipsen, Sanofi, Merck and has participated on a data safety Monitoring Board or Advisory Board of AAA, HutchMed, Merck, Novartis and MSD.

Table 1
Eight key points for SSA use in GEP and Pulmonary NET patients.

Question Number	Content discussed
Q1	Is a positive SSTR-related functional imaging necessary to use an SSA as an antiproliferative agent in daily clinical practice?
Q2	Is there a threshold of Ki-67 to be respected to use an SSA as an antiproliferative treatment in NET in daily clinical practice?
Q3	Is there enough evidence to use an SSA as an adjuvant therapy in NET in daily clinical practice?
Q4	Is there enough evidence to utilize an SSA as maintenance therapy and/or in combination with other anti-tumor therapies in non-functioning NET patients in daily clinical practice?
Q5	Is there enough evidence to use an SSA as antiproliferative therapy in metastatic pulmonary NET in daily clinical practice?
Q6	Is there enough evidence to use above-label dose of octreotide or lanreotide in non-functioning advanced NET progressing on label dose SSA in daily clinical practice?
Q7	Is there enough evidence to use above-label dose of octreotide or lanreotide in functioning NET progressing on label dose SSA in daily clinical practice?
Q8	Is there difference between octreotide and lanreotide in terms of safety and feasibility?

Table 2
Eight key points for SSA use in NET and AIOM/ITANET, ENETS, ESMO guidelines.

Guidelines \ Question	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8
AIOM/ITANET	✓	X	✓	X	✓	X	✓	X
ENETS	✓	X	✓	X	✓	✓	✓	X
ESMO	✓	✓	✓	X/✓	✓	X	✓	X

In this table are reported the eight key points about SSA-related challenging issues for NET, as discussed in this narrative review (Q1 corresponding to Question 1, Q2 to Question 2 and so on). The symbol ✓ indicates that the corresponding key point has been addressed by national Italian (AIOM/ITANET) or international (ENETS/ESMO) guidelines, whereas, the symbol X stands for the lack of a specific indication in the referral guideline.
Abbreviations: AIOM: Italian Association of Medical Oncology; ITANET: Italian Association for Neuroendocrine Tumors; ENETS: European Neuroendocrine Tumor Society; ESMO: European Society for Medical Oncology.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Rindi G, Moch H, McCluggage WG, et al Neuroendocrine neoplasms, non-endocrine organs. In: WHO Classification of Tumours Editorial Board, editor. WHO classification of tumours endocrine and neuroendocrine tumours. 5th ed. Lyon, France: International Agency for Research on Cancer (IARC); 2022.
[2] Nagtegaal ID, Odze RD, Klimstra D, Paradis V, Rugge M, Schirmacher P, et al. The 2019 WHO classification of tumours of the digestive system. Histopathology 2020 Jan;76(2):182–8.
[3] Alcala N, Leblay N, Gabriel AaG, Mangiante L, Hervas D, Giffon T, et al. Integrative and comparative genomic analyses identify clinically relevant pulmonary carcinoid groups and unveil the supra-carcinoids. Nat Commun 2019 Aug 20;10(1):3407.
[4] Kaltsas GA, Besser GM, Grossman AB. The diagnosis and medical management of advanced neuroendocrine tumors. Endocr Rev 2004 Jun;25(3):458–511.
[5] Fraenkel M, Kim M, Faggiano A, de Herder WW, Valk GD, Knowledge NETwork. Incidence of gastroenteropancreatic neuroendocrine tumours: a systematic review of the literature. Endocr Relat Cancer 2014 Jun;21(3):R153–63.

[6] Dasari A, Shen C, Halperin D, Zhao B, Zhou S, Xu Y, et al. Trends in the Incidence, Prevalence, and Survival Outcomes in Patients With Neuroendocrine Tumors in the United States. JAMA Oncol 2017 Oct 1;3(10):1335.

[7] Yao JC, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE, et al. One hundred years after 'carcinoid': epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol 2008 Jun 20;26(18):3063–72.

[8] Oberg K, Krenning E, Sundin A, Bodei L, Kidd M, Tesselaar M, et al. A Delphic consensus assessment: imaging and biomarkers in gastroenteropancreatic neuroendocrine tumor disease management. Endocr Connect 2016 Sep;5(5):174–87.

[9] Stueven AK, Kayser A, Wetz C, Amthauer H, Wree A, Tacke F, et al. Somatostatin Analogues in the Treatment of Neuroendocrine Tumors: Past, Present and Future. Int J Mol Sci 2019 Jun 22;20(12):3049.

[10] Theodoropoulou M, Stalla GK. Somatostatin receptors: from signaling to clinical practice. Front Neuroendocrinol 2013 Aug;34(3):228–52.

[11] Cakir M, Dworakowska D, Grossman A. Somatostatin receptor biology in neuroendocrine and pituitary tumours: part 1–molecular pathways. J Cell Mol Med 2010 Nov;14(11):2570–84.

[12] Günther T, Tulipano G, Dournaud P, Bousquet C, Csaba Z, Kreienkamp HJ, et al. International Union of Basic and Clinical Pharmacology. CV. Somatostatin Receptors: Structure, Function, Ligands, and New Nomenclature. Pharmacol Rev 2018 Oct;70(4):763–835.

[13] Pawlikowski M. The incidence of somatostatin receptors in human neoplasms in the light of ex vivo-in vitro studies. Endokrynol Pol 2006;57(3):238–43.

[14] Reubi J, Waser B, Schaer JC, Laissue JA. Erratum to: Somatostatin receptor sst1-sst5 expression in normal and neoplastic human tissues using receptor autoradiography with subtype-selective ligands. Eur J Nucl Med 2001 Sep;28(9):1433.

[15] Susini C, Buscail L. Rationale for the use of somatostatin analogs as antitumor agents. Ann Oncol 2006 Dec;17(12):1733–42.

[16] Massironi S, Conte D, Rossi RE. Somatostatin analogues in functioning gastroenteropancreatic neuroendocrine tumours: literature review, clinical recommendations and schedules. Scand J Gastroenterol 2016;51(5):513–23.

[17] Msaouel P, Galanis E, Koutsilieris M. Somatostatin and somatostatin receptors: implications for neoplastic growth and cancer biology. Expert Opin Investig Drugs 2009 Sep;18(9):1297–316.

[18] Chalabi M, Duluc C, Caron P, Vezzosi D, Guillermet-Guibert J, Pyronnet S, et al. Somatostatin analogs: does pharmacology impact antitumor efficacy? Trends Endocrinol Metab 2014 Mar;25(3):115–27.

[19] Borna RM, Jahr JS, Kmiecik S, Mancuso KF, Kaye AD. Pharmacology of Octreotide: Clinical Implications for Anesthesiologists and Associated Risks. Anesthesiol Clin 2017 Jun;35(2):327–39.

[20] Astruc B, Marbach P, Bouterfa H, Denot C, Safari M, Vitaliti A, et al. Long-acting octreotide and prolonged-release lanreotide formulations have different pharmacokinetic profiles. J Clin Pharmacol 2005 Jul;45(7):836–44.

[21] Chen T, Miller TF, Prasad P, Lee J, Krauss J, Miscik K, et al. Pharmacokinetics, pharmacodynamics, and safety of microencapsulated octreotide acetate in healthy subjects. J Clin Pharmacol 2000 May;40(5):475–81.

[22] Somatuline® Autogel® lanreotide injection [product monograph]. Ipsen Biopharm Limited, UK, 2015.

[23] Ciccarelli A, Daly A, Beckers A. Lanreotide Autogel for acromegaly: a new addition to the treatment armamentarium. Treat Endocrinol 2004;3(2):77–81.

[24] Cendros JM, Peraire C, Trocóniz IF, Obach R. Pharmacokinetics and population pharmacodynamic analysis of lanreotide Autogel. Metabolism 2005 Oct;54(10):1276–81.

[25] Pavel M, Valle JW, Eriksson B, Rinke A, Caplin M, Chen J, et al. ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Neoplasms: Systemic Therapy - Biotherapy and Novel Targeted Agents. Neuroendocrinology 2017;105(3):266–80.

[26] Pavel M, Öberg K, Falconi M, Krenning EP, Sundin A, Perren A, et al. Gastroenteropancreatic neuroendocrine neoplasms: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2020 Jul;31(7):844–60.

[27] Rinke A, Müller HH, Schade-Brittinger C, Klose KJ, Barth P, Wied M, et al. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. J Clin Oncol 2009 Oct 1;27(28):4656–63.

[28] Caplin ME, Pavel M, Ćwikła JB, Phan AT, Raderer M, Sedláčková E, et al. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. N Engl J Med 2014 Jul 17;371(3):224–33.

[29] Pavel ME, Hainsworth JD, Baudin E, Peeters M, Hörsch D, Winkler RE, et al. Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): a randomised, placebo-controlled, phase 3 study. Lancet 2011 Dec 10;378(9808):2005–12.

[30] Strosberg J, El-Haddad G, Wolin E, Hendifar A, Yao J, Chasen B, et al. Phase 3 Trial of 177Lu-Dotatate for Midgut Neuroendocrine Tumors. N Engl J Med 2017 Jan 12;376(2):125–35.

[31] Halfdanarson TR, Strosberg JR, Tang L, Bellizzi AM, Bergsland EK, O'Dorisio TM, et al. The North American Neuroendocrine Tumor Society Consensus Guidelines for Surveillance and Medical Management of Pancreatic Neuroendocrine Tumors. Pancreas 2020 Aug;49(7):863–81.

[32] Jann H, Denecke T, Koch M, Pape UF, Wiedenmann B, Pavel M. Impact of octreotide long-acting release on tumour growth control as a first-line treatment in neuroendocrine tumours of pancreatic origin. Neuroendocrinology 2013;98(2):137–43.

[33] Annals of Oncology (2021) 32 (suppl_5): S906-S920. 10.1016/annonc/annonc678.

[34] Bongiovanni A, Recine F, Riva N, Foca F, Liverani C, Mercatali L, et al. Outcome Analysis of First-line Somatostatin Analog Treatment in Metastatic Pulmonary Neuroendocrine Tumors and Prognostic Significance of 18FDG-PET/CT. Clin Lung Cancer 2017 Jul;18(4):415–20.

[35] Lenotti E, Alberti A, Spada F, Amoroso V, Maisonneuve P, Grisanti S, et al. Outcome of Patients With Metastatic Lung Neuroendocrine Tumors Submitted to First Line Monotherapy With Somatostatin Analogs. Front Endocrinol (Lausanne) 2021;12:669484.

[36] Faggiano A, Carratù AC, Guadagno E, Tafuto S, Tatangelo F, Riccardi F, et al. Somatostatin analogues according to Ki67 index in neuroendocrine tumours: an observational retrospective-prospective analysis from real life. Oncotarget 2016 Feb 2;7(5):5538–47.

[37] Garcia-Carbonero R, Benavent M, Jiménez Fonseca P, Castellano D, Alonso T, Teule A, et al. A phase II/III randomized double-blind study of octreotide acetate LAR with axitinib versus octreotide acetate LAR with placebo in patients with advanced G1–G2 NETs of non-pancreatic origin (AXINET trial-GETNE-1107). J Clin Oncol 2021;39: 3_suppl:360. https://doi.org/10.1200/JCO.2021.39.3_suppl.360.

[38] Laffi A, Spada F, Bagnardi V, Frassoni S, Pisa E, Rubino M, et al. Gastroenteropancreatic grade 3 neuroendocrine tumors: a single entity or a heterogeneous group? A retrospective analysis J Endocrinol Invest 2022 Feb;45(2):317–25.

[39] Vélayoudom-Céphise FL, Duvillard P, Foucan L, Hadoux J, Chougnet CN, Leboulleux S, et al. Are G3 ENETS neuroendocrine neoplasms heterogeneous? Endocr Relat Cancer 2013 Oct;20(5):649–57.

[40] Lithgow K, Venkataraman H, Hughes S, Shah H, Kemp-Blake J, Vickrage S, et al. Well-differentiated gastroenteropancreatic G3 NET: findings from a large single centre cohort. Sci Rep 2021 Sep 9;11(1):17947.

[41] Niederle B, Pape UF, Costa F, Gross D, Kelestimur F, Knigge U, et al. ENETS Consensus Guidelines Update for Neuroendocrine Neoplasms of the Jejunum and Ileum. Neuroendocrinology 2016;103(2):125–38.

[42] Kulke MH, Siu LL, Tepper JE, Fisher G, Jaffe D, Haller DG, et al. Future directions in the treatment of neuroendocrine tumors: consensus report of the National Cancer Institute Neuroendocrine Tumor clinical trials planning meeting. J Clin Oncol 2011 Mar 1;29(7):934–43.

[43] Barrett JR, Rendell V, Pokrzywa C, Lopez-Aguiar AG, Cannon J, Poultsides GA, et al. Adjuvant therapy following resection of gastroenteropancreatic neuroendocrine tumors provides no recurrence or survival benefit. J Surg Oncol 2020 Jun;121(7):1067–73.

[44] Pavel M, et al. Supplementary Material Gastroenteropancreatic neuroendocrine neoplasms: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2020;31(7):844–60.

[45] Lepage C, Phelip JM, Lievre A, Le-Malicot K, Dahan L, Tougeron D, et al. Lanreotide as maintenance therapy after first-line treatment in patients with non-resectable duodeno-pancreatic neuroendocrine tumours: An international double-blind, placebo-controlled randomised phase II trial - Prodige 31 REMINET: An FFCD study. Eur J Cancer 2022 Nov;175:31–40.

[46] Yordanova A, Wicharz MM, Mayer K, Brossart P, Gonzalez-Carmona MA, Strassburg CP, et al. The Role of Adding Somatostatin Analogues to Peptide Receptor Radionuclide Therapy as a Combination and Maintenance Therapy. Clin Cancer Res 2018 Oct 1;24(19):4672–9.

[47] Sowa-Staszczak A, Stefanska A, Chrapczynski P, Trofimiuk-Müldner M, Szura M, Hubalewska-Dydejczyk A. Does combination of 'cold' and 'hot' somatostatin analogs prolong survival of patients with neuroendocrine neoplasms? Endocr J 2017 Feb 27;64(2):171–7.

[48] Syguła A, Ledwon A, Hasse-Lazar K, Jurecka-Lubieniecka B, Michalik B, Paliczka-Cieślik E, et al. In patients with well-differentiated neuroendocrine tumours, there is no apparent benefit of somatostatin analogues after disease control by peptide receptor radionuclide therapy. Eur J Nucl Med Mol Imaging 2022 Sep;49(11):3841–51.

[49] Rinzivillo M, De Felice I, Magi L, Annibale B, Panzuto F. Octreotide long-acting release (LAR) in combination with other therapies for treatment of neuroendocrine neoplasia: a systematic review. J Gastrointest Oncol 2021 Apr;12(2):845–55.

[50] Yao JC, Lombard-Bohas C, Baudin E, Kvols LK, Rougier P, Ruszniewski P, et al. Daily oral everolimus activity in patients with metastatic pancreatic neuroendocrine tumors after failure of cytotoxic chemotherapy: a phase II trial. J Clin Oncol 2010 Jan 1;28(1):69–76.

[51] Bajetta E, Catena L, Fazio N, Pusceddu S, Biondani P, Blanco G, et al. Everolimus in combination with octreotide long-acting repeatable in a first-line setting for patients with neuroendocrine tumors: an ITMO group study. Cancer 2014 Aug 15;120(16):2457–63.

[52] Bajetta E, Catena L, Pusceddu S, Spada F, Iannacone C, Sarno I, et al. Everolimus in Combination with Octreotide Long-Acting Repeatable in a First-Line Setting for Patients with Neuroendocrine Tumors: A 5-Year Update. Neuroendocrinology 2018;106(4):307–11.

[53] Pusceddu S, Facciorusso A, Giacomelli L, Prinzi N, Corti F, Niger M, et al. Target therapies plus somatostatin analogs in NETs: a network meta-analysis. Endocr Relat Cancer 2021 Jun 17;28(7):467–79.

[54] Hörsch D. Combined lanreotide autogel and temozolomide therapy in progressive neuroendocrine tumours: the SONNET study. Ann Oncol 2016;27(Supplement 6):vi136–48.

[55] Ferolla P, Berruti A, Spada F, Brizzi MP, Ibrahim T, Marconcini R, et al. Efficacy and Safety of Lanreotide Autogel and Temozolomide Combination Therapy in

Progressive Thoracic Neuroendocrine Tumors (carcinoid): Results from the Phase 2 ATLANT Study. Neuroendocrinology 2022 Aug 31.
[56] Baudin E, Caplin M, Garcia-Carbonero R, Fazio N, Ferolla P, Filosso PL, et al. Lung and thymic carcinoids: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up☆. Ann Oncol 2021 Apr;32(4):439–51.
[57] Caplin ME, Baudin E, Ferolla P, Filosso P, Garcia-Yuste M, Lim E, et al. Pulmonary neuroendocrine (carcinoid) tumors: European Neuroendocrine Tumor Society expert consensus and recommendations for best practice for typical and atypical pulmonary carcinoids. Ann Oncol 2015 Aug;26(8):1604–20.
[58] Vesterinen T, Leijon H, Mustonen H, Remes S, Knuuttila A, Salmenkivi K, et al. Somatostatin Receptor Expression Is Associated With Metastasis and Patient Outcome in Pulmonary Carcinoid Tumors. J Clin Endocrinol Metab 2019 Jun 1;104 (6):2083–93.
[59] Dasari A, Bergsland EK, Benson AB, Cai B, Huynh L, Totev T, et al. Treatment Patterns and Clinical Outcomes in Advanced Lung Neuroendocrine Tumors in Real-World Settings: A Multicenter Retrospective Chart Review Study. Oncologist 2019 Aug;24(8):1066–75.
[60] Broder MS, Cai B, Chang E, Neary MP, Papoyan E, Benson AB. Real-World Treatment Patterns for Lung Neuroendocrine Tumors: A Claims Database Analysis. Oncology 2018;94(5):281–8.
[61] Sullivan I, Le Teuff G, Guigay J, Caramella C, Berdelou A, Leboulleux S, et al. Antitumour activity of somatostatin analogues in sporadic, progressive, metastatic pulmonary carcinoids. Eur J Cancer 2017 Apr;75:259–67.
[62] Fazio N, Granberg D, Grossman A, Saletan S, Klimovsky J, Panneerselvam A, et al. Everolimus plus octreotide long-acting repeatable in patients with advanced lung neuroendocrine tumors: analysis of the phase 3, randomized, placebo-controlled RADIANT-2 study. Chest 2013 Apr;143(4):955–62.
[63] Alonso-Gordoa T, Manneh R, Grande E, Molina-Cerrillo J. High-Dose Somatostatin Analogs for the Treatment of Neuroendocrine Neoplasms: where are we Now? Curr Treat Options Oncol 2022 Jul;23(7):1001–13.
[64] Pavel M, Ćwikła JB, Lombard-Bohas C, Borbath I, Shah T, Pape UF, et al. Efficacy and safety of high-dose lanreotide autogel in patients with progressive pancreatic or midgut neuroendocrine tumours: CLARINET FORTE phase 2 study results. Eur J Cancer 2021 Nov;157:403–14.
[65] Chan DL, Ferone D, Albertelli M, Pavlakis N, Segelov E, Singh S. Escalated-dose somatostatin analogues for antiproliferative effect in GEPNETS: a systematic review. Endocrine 2017 Sep;57(3):366–75.
[66] Lamberti G, Faggiano A, Brighi N, Tafuto S, Ibrahim T, Brizzi MP, et al. Nonconventional Doses of Somatostatin Analogs in Patients With Progressing Well-Differentiated Neuroendocrine Tumor. J Clin Endocrinol Metab 2020 Jan 1;105(1).
[67] Panzuto F, Ricci C, Rinzivillo M, Magi L, Marasco M, Lamberti G, et al. The Antiproliferative Activity of High-Dose Somatostatin Analogs in Gastro-Entero-Pancreatic Neuroendocrine Tumors: A Systematic Review and Meta-Analysis. J Clin Med 2022 Oct 18;11(20):6127.
[68] Fazio N., Spada F. Real-word analysis on the use of somatostatin analogs (SSAs) in patients with neuroendocrine neoplasms (NENs): results of a survey conducted by the Italian Society of Medical Oncology (AIOM). AIOM annual conference 2016.
[69] Hofland LJ, Lamberts SWJ. The pathophysiological consequences of somatostatin receptor internalization and resistance. Endocr Rev 2003 Feb;24(1):28–47.
[70] Colao A, Pivonello R, Auriemma RS, Galdiero M, Savastano S, Lombardi G. Beneficial effect of dose escalation of octreotide-LAR as first-line therapy in patients with acromegaly. Eur J Endocrinol 2007 Nov;157(5):579–87.
[71] Ferolla P, Faggiano A, Grimaldi F, Ferone D, Scarpelli G, Ramundo V, et al. Shortened interval of long-acting octreotide administration is effective in patients with well-differentiated neuroendocrine carcinomas in progression on standard doses. J Endocrinol Invest 2012 Mar;35(3):326–31.
[72] Chadha MK, Lombardo J, Mashtare T, Wilding GE, Litwin A, Raczyk C, et al. High-dose octreotide acetate for management of gastroenteropancreatic neuroendocrine tumors. Anticancer Res 2009 Oct;29(10):4127–30.
[73] Strosberg J, Weber J, Feldman M, Goldman J, Almhanna K, Kvols L. Above-Label Doses of Octreotide-LAR in Patients With Metastatic Small Intestinal Carcinoid Tumors. Gastrointest Cancer Res 2013 May;6(3):81–5.
[74] Al-Efraij K, Aljama MA, Kennecke HF. Association of dose escalation of octreotide long-acting release on clinical symptoms and tumor markers and response among patients with neuroendocrine tumors. Cancer Med 2015 Jun;4(6):864–70.
[75] Panzuto F, Magi L, Rinzivillo M. Exocrine pancreatic insufficiency and somatostatin analogs in patients with neuroendocrine neoplasia. Expert Opin Drug Saf 2021 Apr;20(4):383–6.
[76] Koffas A, Toumpanakis C. Comparative safety review of the current therapies for gastroenteropancreatic neuroendocrine tumors. Expert Opin Drug Saf 2021 Mar;20 (3):321–34.
[77] Raj N, Cruz E, O'Shaughnessy S, Calderon C, Chou JF, Capanu M, et al. A Randomized Trial Evaluating Patient Experience and Preference Between Octreotide Long-Acting Release and Lanreotide for Treatment of Well-Differentiated Neuroendocrine Tumors. JCO Oncol Pract 2022 Sep;18(9): e1533–41.
[78] Adelman D, Truong Thanh XM, Feuilly M, Houchard A, Cella D. Evaluation of Nurse Preferences Between the Lanreotide Autogel New Syringe and the Octreotide Long-Acting Release Syringe: An International Simulated-Use Study (PRESTO). Adv Ther 2020 Apr;37(4):1608–19.
[79] O'Toole D, Kunz PL, Webb SM, Goldstein G, Khawaja S, McDonnell M, et al. PRESTO 2: An International Survey to Evaluate Patients' Injection Experiences with the Latest Devices/Formulations of Long-Acting Somatostatin Analog Therapies for Neuroendocrine Tumors or Acromegaly. Adv Ther 2022 Dec;11: 1–20.