

ENETS Consensus Guidelines Update for the Management of Distant Metastatic Disease of Intestinal, Pancreatic, Bronchial Neuroendocrine Neoplasms (NEN) and NEN of Unknown Primary Site

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Introduction

The goal of this paper is to update a more extensive review and guidelines paper published in 2012 [1]. Generally, any pertinent update pertaining to the diagnosis and staging of individual primary tumors is provided in the relevant papers published elsewhere in this issue of updated guideline reviews. More specific issues with respect to therapy of stage IV neuroendocrine neoplasms (NEN) (focusing on grade 1/2 tumors) are given below. A separate guideline is provided for poorly differentiated neoplasms (grade 3 NEN). As some new large phase III trials have been published since the previous guidelines, this has indeed led to specific modifications in our approach to therapy.

Metastatic disease from NEN is very prevalent in intestinal and pancreatic NEN [2–4]. At initial diagnosis, 40–50% of NEN patients present with distant metastases,

with increasing prevalence over time depending on initial disease stage. Metastases are predominantly found in the liver and/or lymph nodes. In contrast, bone metastases are reported in <15% of cases [5, 6]; however, the true prevalence of bony metastases is probably underestimated, since the reported figures are not based on the most sensitive imaging methods such as bone MRI or ⁶⁸Ga-DOTATOC/NOC/TATE PET/CT. Other rare disease sites include the lung, brain and peritoneum, which have also been covered in guidelines [6–9].

Treatment options in metastatic disease consist of liver surgery and/or locoregional and ablative therapies (fig. 1). In general, these approaches are followed if extrahepatic disease is excluded or, in functional tumors, if the major tumor burden is located in the liver. Due to

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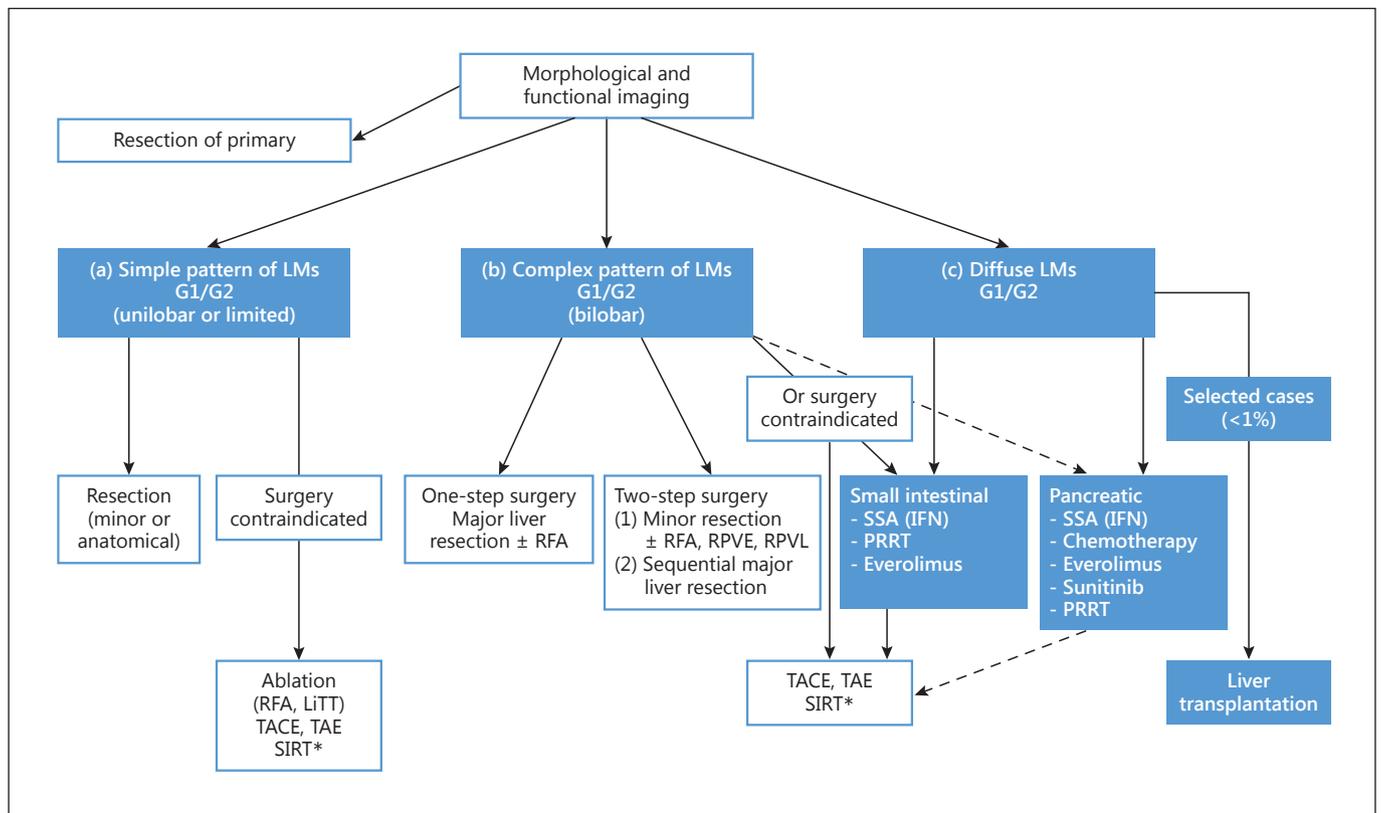


Fig. 1. Management of liver metastases without extrahepatic disease in G1/G2 NEN. * SIRT (selective internal radiation therapy) is still an investigational method. LiTT = Laser-induced thermotherapy; LMs = liver metastases; RFA = radiofrequency ablation; RPVE = right portal vein embolization; RPVL = right portal vein ligation; TACE = transarterial chemoembolization; TAE = transarterial embolization.

the rarity of the disease, the number of prospective randomized trials is limited, and most recommendations are based on uncontrolled studies, representing expert opinions. This is especially true for surgical treatment, different locoregional or ablative therapies [embolization, chemoembolization, radiofrequency ablation and selective internal radiation therapy (SIRT)] and systemic chemotherapy. Somatostatin analogues (SSA) and novel targeted drugs, such as the multiple tyrosine kinase inhibitor sunitinib and the mTOR inhibitor everolimus, are the only drugs that have been evaluated in NEN within placebo-controlled trials. Based on the results of these trials, SSA, sunitinib and everolimus have been approved and registered for antiproliferative therapy in different neuroendocrine tumor (NET) subtypes excluding neuroendocrine carcinoma (NEC). Recent data from a placebo-controlled trial with lanreotide (CLARINET study) in enteropancreatic NET have provided novel evidence for the antiproliferative activity of

SSA. Furthermore, it has recently been reported that three large randomized controlled drug trials (i.e. everolimus vs. placebo in lung and intestinal NET and NET of unknown primary tumor, RADIANT-4; ¹⁷⁷Lu-DOTATATE vs. high-dose octreotide in midgut NET, NETTER-1, and telotristat etiprate vs. placebo in refractory carcinoid syndrome, TELESTAR) have reached their primary endpoints [10–12]. These well-constructed phase III trials in NET have an impact on the current treatment recommendations and therapeutic algorithm. In addition, there is novel information available on the use of targeted drugs from application outside of randomized clinical trials.

Given the variety of treatment options, the heterogeneity of NEN and the individual disease complexity, it is strongly recommended if not mandatory to discuss NEN patients after accurate imaging and pathology review in a multidisciplinary tumor board for appropriate therapeutic decision making, especially to exploit surgical therapy

Table 1. Therapeutic options and conditions for preferential use as first-line therapy in advanced NEN

Drug	Functionality	Grading	Primary site	SSTR status	Special considerations
Octreotide	+/-	G1	midgut	+	low tumor burden
Lanreotide	+/-	G1/G2 (-10%)	midgut, pancreas	+	low and high (>25%) liver tumor burden
IFN-alpha 2b	+/-	G1/G2	midgut		if SSTR negative
STZ/5-FU	+/-	G1/G2	pancreas		progressive in short-term* or high tumor burden or symptomatic
TEM/CAP	+/-	G2	pancreas		progressive in short-term* or high tumor burden or symptomatic; if STZ is contraindicated or not available
Everolimus	+/-	G1/G2	lung		atypical carcinoid and/or SSTR negative
			pancreas		insulinoma or contraindication for CTX
			midgut		if SSTR negative
Sunitinib	+/-	G1/G2	pancreas		contraindication for CTX
PRRT	+/-	G1/G2	midgut	+	extended disease; extrahepatic disease, e.g. bone metastasis
Cisplatin [§] /etoposide	+/-	G3	any		all poorly differentiated NEC

CAP = Capecitabine; TEM = temozolomide. * ≤6–12 months. [§] Cisplatin can be replaced by carboplatin.

in potentially resectable NEN patients and explore locoregional therapies upfront. Choosing antiproliferative therapies is also challenging depending on the tumor primary, its functional status, its growth rate, grade and overall disease burden and the goal of individual therapies within the patient's choice and status. Variation of treatment choices will also depend on physician expertise, the complexity of the treatment center and access to novel treatments. Recommendations for the preferential use of targeted drugs or chemotherapy as first-line therapy are summarized in table 1.

This review focuses on intestinal and pancreatic NEN, and it provides a therapeutic algorithm for both subtypes (fig. 2, 3). The management of typical and atypical lung NET is similar to that of gastroenteropancreatic (GEP) NEN taking into consideration pathological features (mitotic count, Ki-67), somatostatin receptor (SSTR) expression, growth rate and disease extent. The best practice recommendations for the management of typical and atypical bronchial NET are reported in a separate recently published ENETS consensus paper [13].

Therapeutic Options

In grade 1 (G1) and G2 NET, surgery with curative intent always has to be considered, even if liver and/or lymph node metastases are present (fig. 1). In non-resectable disease, the following treatment options should be considered to control symptoms secondary to the hypersecretion of peptide hormones/amines leading to a functional syndrome (carcinoid syndrome, diarrhea and other symptoms related to functionally active pancreatic NEN) and/or tumor growth control. In some patients, it may be necessary to combine therapies for example to suppress symptoms using SSA in addition to locoregional therapies or other antiproliferative agents.

Locoregional Therapies

In the absence of any large comparative trials of different locoregional or ablative therapies (bland embolization, chemoembolization, radioembolization, radiofrequency ablation or microwave destruction) or systemic treatment, the choice of treatment is based on individual patient features (e.g. size, distribution and

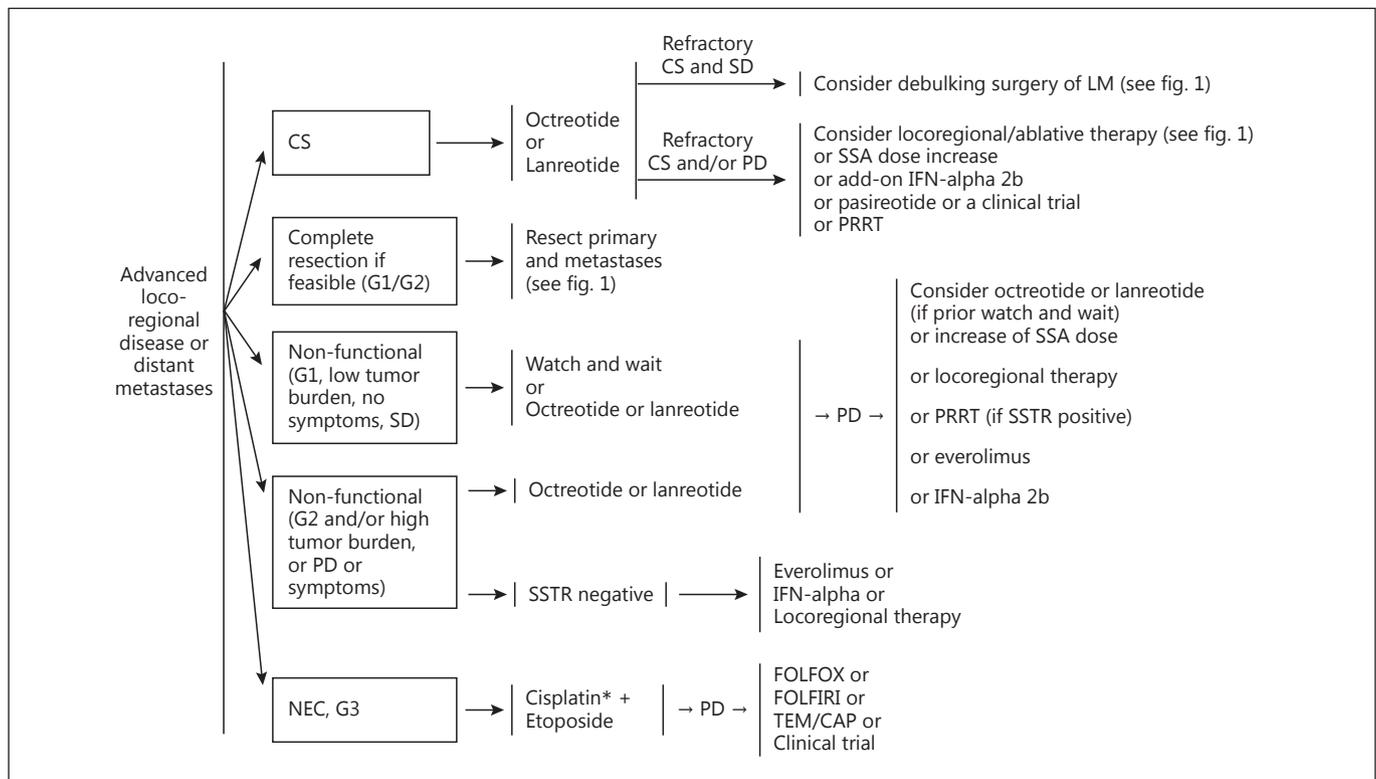


Fig. 2. Therapeutic algorithm for the management of intestinal (midgut) NEN with advanced locoregional disease and/or distant metastases. CS = Carcinoid syndrome; LM = liver metastasis; PD = progressive disease; SD = stable disease; TEM/CAP = temozolomide/capecitabine. * Cisplatin may be replaced by carboplatin.

number of liver lesions, vascularization, proliferative index) and local physicians' expertise [14]. Locoregional therapies should be exploited early, following SSA therapy, to prevent carcinoid crisis in functionally active NET (especially midgut NET with classical carcinoid syndrome), and they may be an alternative option to systemic therapies in patients with non-functional tumors if the disease is limited to the liver. Locoregional therapies may be considered repetitively during the course of the disease. There is consensus that SIRT is still investigational, and that a comparative trial of SIRT to bland embolization is required, as well as more safety data on long-term tolerability of SIRT to establish this procedure for the management of NEN [14–18].

Debulking Surgery

This is an alternative option to locoregional therapies and could be considered in patients with uncontrolled functional tumors, especially in patients with carcinoid syndrome, refractory insulinoma, glucagonoma or vipoma or PTH-related peptide-secreting tumors. Debulking

surgery may be considered in patients with non-functional tumors if the disease is not progressive over a 6-month period and the patients are suffering from symptoms related to tumor burden. Although some retrospective studies indicate that surgery for liver metastasis is associated with improved survival [19–22], it remains unclear whether debulking surgery is of benefit in asymptomatic patients, since comparative trials to systemic therapy are lacking. Even if surgery is performed with curative intent, there is a high rate of disease recurrence within 3–5 years [4, 23]. In patients with carcinoid syndrome, it is important to control the hypersecretion of serotonin with SSA prior to surgery, in order to prevent carcinoid crisis.

Liver Transplantation

Transplantation is generally not recommended as a treatment option in advanced NEN; it may be an option in highly selected patients with carcinoid syndrome or other functional NET and extended liver disease, early refractory to multiple systemic treatments including SSA, interferon (IFN)-alpha, locoregional therapies and pep-

tide receptor-targeted radiotherapy (PRRT) [4]. A precise preselection of patients (e.g. well-differentiated NET, the exclusion of extrahepatic disease by optimized staging, low serum total bilirubin) for liver transplantation may increase the 5-year survival rates in patients with NET undergoing liver transplantation [24–26].

Minimal Consensus Statement on Therapeutic Options

Surgery with curative intent and/or locoregional or ablative therapies should be considered at initial diagnosis and during the course of the disease as an alternative approach to systemic therapies. In patients with functional NET, all liver-directed therapies require the prior initiation of SSA therapy (or other specific symptom-controlling measures). Debulking surgery is indicated in selected patients with functional NET with predominant liver disease for improved syndrome control, even if the liver tumor burden can be reduced by <90%. Liver transplantation is an option in highly selected patients, preferably in young patients with functional syndromes demonstrating early resistance to medical therapy.

Systemic Therapy

SSA and Novel Compounds for Syndrome Control

SSA are first-line therapy in functionally active NEN including tumors associated with the carcinoid syndrome and functionally active endocrine pancreatic NET (such as vipoma and glucagonoma). The commercially available agents octreotide and lanreotide are considered equally effective for symptom control. In general, long-acting formulations (octreotide LAR 10–30 mg i.m. per month; lanreotide autogel 60–120 mg deeply s.c. per month) are used over a medium- to long-term period. Initiating therapy with a lower dose of the long-acting formulations or with octreotide 50–100 µg s.c. for 7–10 days twice to thrice per day is recommended [27–29], particularly in patients with severe symptoms.

In case of refractory syndrome, dose escalation above the upper labeled dosages is an option [30, 31]. In general, dose escalation is performed by shortening the injection interval from 4 to 3 weeks with long-acting SSA. There is consensus that dose escalation can be recommended in refractory carcinoid syndrome for improvement of symptoms.

Pasireotide is a novel universal somatostatin ligand that binds to 4 of 5 SSTR and that is not approved for the treatment of carcinoid syndrome or other functional NEN, but for the treatment of pituitary tumors associated

with Cushing's disease or acromegaly. In a phase II trial, 27% of patients with carcinoid syndrome showed symptom improvement with pasireotide following failure with standard doses of octreotide LAR [32]; however, in a comparative trial, pasireotide LAR 60 mg was not superior to octreotide LAR 40 mg/month [33]. Since there are limited treatment options available in refractory carcinoid syndrome, pasireotide might be considered in individual highly selected patients when other treatments failed or are not feasible depending on accessibility, and this includes locoregional therapies, debulking surgery, IFN-alpha and novel drugs in clinical trials.

Telotristat etiprate, an oral serotonin synthesis inhibitor, is a potential novel option in refractory carcinoid syndrome [34, 35]. In a phase III placebo controlled trial (TELESTAR), telotristat etiprate significantly reduced diarrhea in patients with refractory carcinoid syndrome while on SSA [12]. If approved, telotristat etiprate can be recommended in addition to SSA for refractory diarrhea in carcinoid syndrome patients.

SSA for Tumor Growth Control

SSA are an established therapy for antiproliferative purposes in intestinal NET, based on 2 placebo-controlled trials (the PROMID study and the CLARINET study). Both drugs, octreotide LAR and lanreotide autogel, are recommended as first-line systemic therapy in midgut NET to control tumor growth [36, 37]. There is consensus that SSA can be used as first-line systemic therapy in pancreatic NET (Ki-67 <10%) in view of lack of toxicity, and although the antiproliferative effects of SSA are considered a drug class effect, based on the CLARINET study, lanreotide autogel should preferably be used in pancreatic NET, since prospective data on the use of octreotide LAR in pancreatic NET are lacking [37, 38]. There are retrospective data supporting the use of octreotide LAR in low-grade pancreatic NET [39].

SSA can be recommended for the prevention or inhibition of tumor growth in both intestinal and pancreatic NET. Equally, based on the CLARINET study, the use of SSA in GEP NET is recommended up to a Ki-67 of 10% [37]. However, for the overall group of NEN, there was no consensus among experts on a clear cut-off value for the recommendation of SSA for antiproliferative purposes. When considering SSA as first-line therapy in intestinal or pancreatic NET, some experts feel that 5% might be a more appropriate Ki-67 cut-off threshold. Prospective validation is required to determine the appropriate Ki-67 value for treatment stratification to SSA or more aggressive therapies.

The recommendation for the use of SSA expands to patients with higher hepatic tumor burden (>25% liver involvement) as supported by a subgroup analysis from the CLARINET study [37]. Although no benefit in overall survival could be demonstrated by the placebo-controlled trials with SSA that allowed cross-over from the placebo arm upon progression to open-label SSA, it is expected that the use of SSA has an impact on the outcome of patients [40]. It remains, however, controversial if SSA should be started at initial diagnosis or after the observation of spontaneous tumor growth and be initiated in case that disease progression occurs. There is consensus that SSA should be started at diagnosis in cases of high liver tumor burden and extended disease, since these are worse prognostic factors. Another factor in favor of early SSA therapy is a pancreatic primary, given the fact that the overall 5-year survival rate in stage IV disease does not exceed 40–60% [41, 42]. There is no data to support continued use of SSA when patients progress on SSA (they may be required, however, for the continued suppression of functionally active tumors).

SSA may also be used in NET of other sites (e.g. rectal or bronchial NET), when the SSTR status is positive (on somatostatin imaging or histology), if the tumor is slowly growing, G1 or G2 and preferably with Ki-67 <10%. Prospective ongoing clinical trials need to further evaluate the role of SSA (lanreotide autogel and pasireotide, respectively) in typical and atypical lung NEN (www.clinicaltrials.gov).

SSA may be considered in SSTR-negative NEN, if a small volume disease is present and it is expected that imaging may have provided false negative information on SSTR status. Immunostaining with SSTR2 antibodies may also be useful [43, 44].

Minimal Consensus Statement on Systemic Therapy

SSA, octreotide and lanreotide, are effective drugs for syndrome control in functional NET. In refractory carcinoid syndrome or with insufficient syndrome control in pancreatic NET, a dose escalation of SSA may be recommended. The novel SSA pasireotide might be considered in refractory carcinoid syndrome in case all other treatment options including ablative procedures, transarterial embolization and IFN-alpha have failed, and there is no clinical trial available. If approved, the oral serotonin synthesis inhibitor telotristat etiprate will offer a novel treatment option in refractory carcinoid syndrome.

For antiproliferative purposes, SSA may be used in stable or progressive disease or in patients with unknown tumor behavior. SSA are recommended as a first-line therapy in midgut NET and can be considered in pancreatic NET as a first-line therapy (up to a Ki-67 of 10%). While the antiproliferative efficacy of both available SSA is considered a drug class effect, there is a higher

level of evidence for the use of lanreotide autogel in pancreatic NET; and based on the respective study designs, octreotide LAR is approved for tumor control in midgut NET, whereas lanreotide autogel is approved for enteropancreatic NET. SSA may be considered in low-grade NET of other sites. There is no established Ki-67 threshold for the use of SSA, preferably SSA should be used if Ki-67 is ≤10%.

Interferon-Alpha

IFN-alpha is a second-line therapy in NEN that are functionally active. It is recommended to use IFN-alpha as add-on therapy to SSA therapy in functional tumors. The recommended dose of IFN-alpha 2b is 3 × 3 to 3 × 5 MU/week s.c. [28, 45]. In patients who do not tolerate the conventional regimen, alternatively pegylated IFN-alpha (50–180 µg/week s.c.) can also be used [46]. IFN-alpha has antiproliferative activity and may be considered for antiproliferative purposes if other approved drugs are unavailable especially in midgut NEN. IFN-alpha has been explored in comparison to bevacizumab for antiproliferative purposes in a large randomized trial of 400 patients with carcinoids (including different primary sites) who received octreotide LAR concomitantly (SWOG trial); the primary endpoint, median progression-free survival (PFS), was not different between those taking IFN-alpha and those taking bevacizumab [47]. This study, however, confirms the antiproliferative activity of IFN-alpha 2b in advanced G1/G2 NET, NET with progressive disease or with other poor prognostic features with a median PFS of 15.4 months reached in the IFN-alpha arm.

Minimal Consensus Statement

IFN-alpha is an established and approved therapy for syndrome control, and primarily used as second-line (add-on) therapy in refractory carcinoid syndrome or functional pancreatic NET. IFN is an option for inhibiting tumor growth and, due to limited therapy options in midgut NET, it may be considered an antiproliferative option (less so in pancreatic NET).

Novel Targeted Drugs

Novel targeted drugs (everolimus and sunitinib) are approved for pancreatic NET based on the results of two placebo-controlled trials on progressive pancreatic NET. The median PFS is around 11 months with either of the drugs, while tumor remission occurs in 5% and <10% of the patients with everolimus and sunitinib, respectively. The use of either everolimus or sunitinib is recommended in progressive G1/G2 pancreatic NET, irrespective of Ki-67 and tumor burden. The standard dose for everolimus is 10 mg/day and for sunitinib 37.5 mg/day as continuous treatment. Side effects may re-

quire a dose reduction to 5 mg/day for everolimus or to 25 mg/day for sunitinib [48, 49]. While comparative data of both drugs are lacking, the selection of the targeted drug is based on the medical history of the patient, the side effect profile of the drug and accessibility to the treatment.

Targeted drugs, everolimus or sunitinib, are one of the different treatment options in pancreatic NET and may be used as first- or second-line options with respect to chemotherapy or subsequent to SSA therapy (table 1). Although targeted drugs may be the first therapy choice in pancreatic NET, there is consensus that targeted drugs *should not* be broadly used as first-line therapy for their potential toxicity. There is no evidence on the exact sequencing of different treatment options in pancreatic NET. Potential toxicity needs to be considered when sequencing therapies, as indicated in a retrospective multicenter study on 169 patients from Italy, where a markedly increased toxicity was reported with everolimus in patients previously treated either with PRRT and/or chemotherapy [50]. In contrast, a smaller retrospective study from the Netherlands on 24 patients indicated that the safety of everolimus is not influenced by previous PRRT [51]. An ongoing trial (SEQTOR) is currently investigating the antiproliferative efficacy of everolimus versus streptozotocin with 5-fluorouracil (STZ/5-FU) in progressive pancreatic NET in a crossover design upon progression (www.clinicaltrials.gov).

Everolimus can be recommended in advanced NET of non-pancreatic origin in case of disease progression (e.g. NET of intestinal or lung origin). It can be used in midgut NET as second- or third-line therapy after failure of SSA and/or IFN-alpha or PRRT. This recommendation is based on the results of the RADIANT-4 trial [10] that reached its primary endpoint and demonstrates superior PFS with everolimus compared to placebo in non-functional NET of intestinal or lung origin; and it is supported by the RADIANT-2 trial on advanced NET associated with the carcinoid syndrome (that tended towards similar results) [52].

The sequencing of everolimus as second- or third-line therapy for advanced intestinal NET also depends on other issues, including accessibility of PRRT. Individual patient selection is important. A strong SSTR expression on imaging is necessary to achieve better results with PRRT, while extensive hepatic and/or bone disease as well as decreased kidney function may limit its use. Otherwise, the use of everolimus may be limited by comorbidities such as uncontrolled diabetes or lung diseases. A comprehensive review of the patients' medical history, pathology and

imaging has an impact on therapy allocation to either everolimus or PRRT after failure of SSA.

In the absence of approved drugs in metastatic lung NET, everolimus may be recommended as a first-line therapy in progressive disease. However, in patients with low proliferative activity (G1, typical carcinoid) with strong SSTR expression on imaging, SSA may be considered as a first-line therapy. Although comprehensive clinical data are lacking for the use of SSA in lung NET, it is expected that the clinical behavior of typical carcinoids (mitotic count <2/10 HPF; G1 NET) is similar to G1 NET of other sites. Ongoing and planned clinical trials (LUNA; lanreotide vs. placebo) will further elucidate the role of SSA in advanced lung NET (www.clinicaltrials.gov).

There is not sufficient data to support the use of other targeted drugs including bevacizumab, sorafenib, pazopanib or axitinib in either pancreatic or non-pancreatic NEN. These drugs as well as sunitinib in midgut NET (SUNLAND study) are currently explored in prospective randomized clinical trials, but their results are not yet available and their use should be restricted to clinical trials.

It is standard practice to combine targeted drugs with SSA in functionally active NEN. The aim of a combination therapy of everolimus and SSA may not only be tumor growth inhibition, but also improved syndrome control, e.g. in patients with recurrent hypoglycemia related to metastatic insulinoma. Although prospective trials with everolimus are lacking to demonstrate an improvement of hormone-related syndromes, the early use of everolimus may be justified to avoid hospitalization and sequelae related to hypoglycemia based on the experience in few patients (fig. 3).

Although there might be a rationale to combine targeted drugs with SSA also in non-functional NET, given the SSTR expression in the majority of NET patients, there is no robust evidence yet that the combination therapy of targeted drugs with SSA is superior to monotherapy with either everolimus or sunitinib for antiproliferative purposes. A comparative trial on progressive pancreatic NET (COOPERATE-2) with everolimus versus everolimus and pasireotide, a novel SSA with a broader binding affinity to SSTR compared to first-generation SSA, failed to demonstrate superiority of the combination therapy with respect to PFS [53]. Although there might be a potential benefit of a combination therapy using other SSA, such as lanreotide or octreotide, and a recent open-label phase II study indicates favorable response (disease control rate >90%) with everolimus in combination with octreotide in a first-line setting in GEP NET

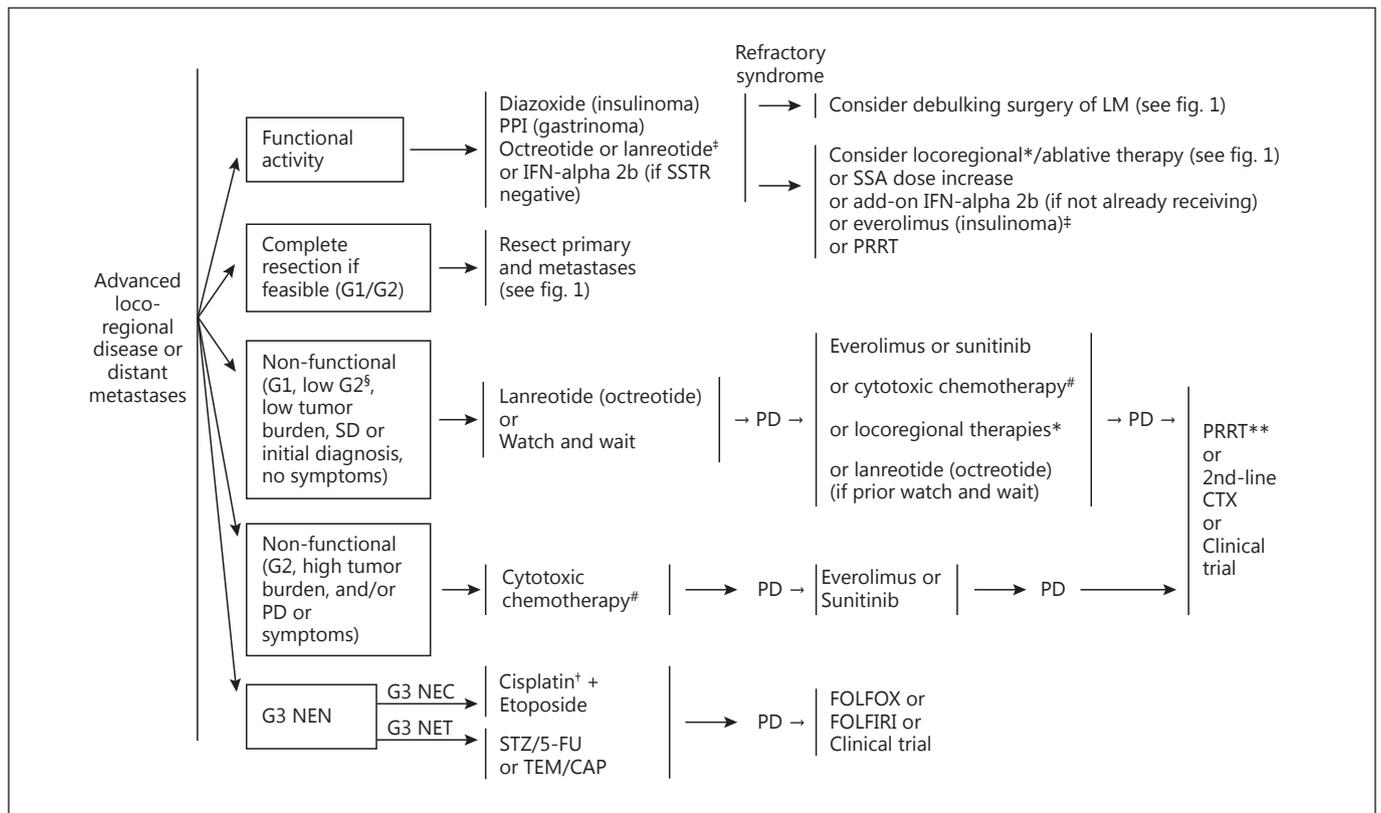


Fig. 3. Therapeutic algorithm for the management of pancreatic NEN with advanced loco-regional disease and/or distant metastases. [§] Ki-67 <5–10%; * locoregional therapies are contraindicated after Whipple procedure; # recommended chemotherapy includes STZ/5-FU or STZ/doxorubicin; TEM/CAP is an alternative chemotherapy regimen if STZ-based chemotherapy is not available; ** if SSTR imaging is positive; † patients should be closely monitored for paradoxical reaction (increasing hypoglycemia); ‡ cisplatin may be replaced by carboplatin; G3 NET is coined for tumors with Ki-67 >20% but well- or moderately differentiated morphol-

ogy. 5-FU = 5-Fluorouracil; CS = carcinoid syndrome; CTX = chemotherapy; LM = liver metastasis; PD = progressive disease; SD = stable disease; TEM/CAP = temozolomide/capecitabine. The term ‘or’ indicates that the use of the other options at further progression should be considered, e.g. patients with G1 or low-grade G2 NET and/ or low tumor burden who received everolimus may be treated with standard cytotoxic chemotherapy upon progression before unapproved drugs, second-line chemotherapy or a clinical trial is considered.

[54], in the absence of a comparative study of targeted drugs with either octreotide or lanreotide compared to the targeted drug alone, the upfront combination therapy of targeted drugs with SSA cannot be recommended. Furthermore, data are lacking to support the use of SSA beyond progression in combination with targeted drugs.

Minimal Consensus Statement

Everolimus and sunitinib are approved antiproliferative therapies in progressive pancreatic NET, and they represent one of the different treatment options next to SSA and systemic chemotherapy. They can be considered as a first-line therapy, especially if SSA is not an option, and if systemic chemotherapy is not clinically required, not feasible or not tolerated. Everolimus or sunitinib

are generally recommended after failure of SSA or chemotherapy in pancreatic NET. In intestinal NET, everolimus may be used as a second-line therapy after failure of SSA or as a third-line therapy after failure of PRRT; while in progressive lung NET, everolimus is recommended as a first-line therapy, unless SSA may be considered as a first-line therapy (e.g. in typical carcinoid with slow growth expressing SSTR). The combined use of targeted drugs with SSA for antiproliferative purpose is not recommended in non-functional NET. Antiangiogenic drugs including sunitinib are not recommended in non-pancreatic NEN outside of clinical trials.

Systemic Chemotherapy

Systemic chemotherapy is indicated in progressive or bulky pancreatic NET and in G3 NEN. The term G3 NEN

comprises well- or moderately differentiated tumors with Ki-67 >20% that are not termed in the WHO 2010 classification and large or small cell tumors with Ki-67 >20% (G3 NEC; presented in detail elsewhere). Chemotherapy may be considered in NET of other sites (lung, thymus, stomach, colon or rectum) under certain conditions [e.g. when Ki-67 is at a high level (upper G2 range), in rapidly progressive disease and/or after failure of other therapies, or if SSTR imaging is negative].

Chemotherapy is one of different treatment options in pancreatic NET and can be used in G1 or G2 tumors. Cytotoxic therapy combinations include: STZ/5-FU (an established therapy) and doxorubicin with STZ as an alternative option; however, the use of doxorubicin is limited by a cumulative dose of 500 mg/m² (due to the risk of cardiotoxicity). Therapeutic regimens can be recommended according to Moertel et al. (cycles every 6 weeks) or Fjallskog et al. (cycles every 3 weeks) [55–57]. Data do not support three-drug regimen associations including cisplatin, nor the replacement of 5-FU by capecitabine [58–60]. Systemic chemotherapy may be considered without prior progression in patients with high tumor burden. There is no established Ki-67 cut-off value for the recommendation of chemotherapy. Patients with pancreatic NET with Ki-67 of 5–20% can be treated with chemotherapy. Other factors that favor chemotherapy compared to targeted drugs include: bulky disease; a symptomatic patient; rapid tumor progression in ≤6–12 months, and patients with a possible chance of achieving a response to allow for surgery (neoadjuvant option).

Although replacing STZ/5-FU by temozolomide/capecitabine is gaining popularity, this approach cannot be categorically recommended, since data for temozolomide are still limited. However, temozolomide +/- capecitabine may be considered as an alternative regimen depending on the availability of STZ/5-FU. Reported objective response rates from small prospective and retrospective studies achieved with temozolomide either combined with antiangiogenic drugs or capecitabine range between 15 and 70% [61–63]. The value of temozolomide either as mono- or combination therapy with capecitabine or antiangiogenic drugs is further explored in prospective clinical trials (www.clinicaltrials.gov). Few studies indicate that the MGMT status is correlated with tumor response to alkylating agents [64–66]; however, determining MGMT expression or methylation can currently not be recommended as selection criterion for the use of chemotherapy in NEN, since studies are small, and prospective validation is lacking.

After failure of STZ-based chemotherapy in pancreatic NET, the following are alternative chemotherapeutic options: temozolomide +/- capecitabine and oxaliplatin-based chemotherapy + 5-FU or capecitabine. It remains unclear which treatment option is superior; however, in pancreatic NET there are data supporting the preferential use of temozolomide +/- capecitabine with promising response rates and a low toxicity profile [62, 67, 68].

Systemic chemotherapy is not recommended in non-pancreatic NET unless G2 NET (Ki-67 >15%), tumors displaying aggressive biological behavior (RECIST progression in 3–6 months) or in those which are SSTR negative. Metronomic chemotherapy may be an option using temozolomide and/or capecitabine +/- SSA in G2 NET or in SSTR-negative NET, or capecitabine + bevacizumab after failure of other treatments (such as locoregional therapies, IFN-alpha or everolimus) [69–72]. Given the limited treatment options in bronchial carcinoids, temozolomide is a therapeutic option based on data from small studies [73, 74]. Prospective validation is needed, as well as evaluation of the best sequencing of therapies in bronchial NET including SSA, everolimus and temozolomide.

In G3 NEC, cisplatin-based chemotherapy (e.g. cisplatin/etoposide) is standard therapy and recommended as a first-line therapy (see guidelines on poorly differentiated tumors). Cisplatin might be replaced by carboplatin, based on the data from the Nordic NEC trial [75]. Although objective remission rates are high (40–67%), the median PFS is limited with 4–6 months [76–78]. Second-line systemic therapy options include FOLFOX and FOLFIRI [79, 80], while topotecan is not effective in G3 NEC [81]. Temozolomide-based chemotherapy should be preferably used in pancreatic G3 NET or in gastrointestinal NEC with Ki-67 <55% [67, 78]; prospective studies are underway to assess the activity of temozolomide in this setting. Targeted drugs in combination with chemotherapy are under evaluation in clinical trials on G3 NEN. Further details on the management of G3 NEN, including recommendations for different primary tumor sites, are summarized in a recently published comprehensive review on G3 NEC and are provided in a separate consensus paper [82, 83].

Minimal Consensus Statement

STZ-based chemotherapy is one of the treatment options in pancreatic G1/G2 NET next to SSA and novel targeted drugs. It is preferably recommended in patients with higher tumor burden with or without associated clinical symptoms and/or in patients with significant tumor progression in ≤6–12 months. Although data for temozolomide-based chemotherapy are still limited, it may replace the STZ/5-FU regimen in case this is not available,

in pancreatic NET and it may be considered in G3 NET and in high-risk NET of other primary site (e.g. pulmonary NET). In G3 NEC, platinum-based chemotherapy is recommended as a first-line therapy.

Peptide Receptor Radionuclide Therapy

PRRT is a therapeutic option in progressive SSTR-positive NET with homogenous SSTR expression (all lesions are positive). In general, the use of PRRT follows failed first-line medical therapy. Radionuclide therapy with either ^{90}Y and/or ^{177}Lu -labeled SSA is most frequently used in NET, but ^{177}Lu -labelled SSA is increasingly used due to lower kidney toxicity. The minimum requirements for PRRT are reported in a separate consensus guideline [84]. Until recently, there were no results from prospective randomized trials available. The registrational trial of ^{177}Lu -DOTATATE in progressive midgut NET (NETTER-1) has reached its primary endpoint with a significant prolongation of PFS compared to high-dose octreotide (60 mg/month). Based on this trial, and cumulative data from prospective and retrospective trials over the last 15 years, PRRT may be recommended in midgut NET as a second-line therapy after failure of SSA if the general requirements for applying PRRT are fulfilled [84–87] or as a third-line therapy after failure of everolimus.

Given the different established and approved therapeutic options in pancreatic NET and the lack of a prospective trial with PRRT in pancreatic NET, PRRT (if available) is in general recommended in G1/G2 NET after failure of medical therapy including SSA, chemotherapy or novel targeted drugs. However, potential increasing toxicity, e.g. after prior chemotherapy or targeted therapy, needs to be considered, requires close surveillance and might justify an earlier use of PRRT in selected patients (table 1).

Minimal Consensus Statement

PRRT is recommended after failure of medical therapy. Data from a prospective trial in midgut NET support its role as a second-line therapy option in intestinal NET if the general requirements for PRRT are fulfilled and as an alternative option to everolimus. The optimal sequencing with targeted drugs and/or chemotherapy needs to be defined in pancreatic NET when data from prospective randomized trials with PRRT in pancreatic NET become available.

Management of NET with Unknown Primary Tumor

In approximately 13% of patients who are diagnosed as having NEN, the primary site is not known. In patients with unknown primary tumor, the site is most frequently

localized in the intestine or the lung. Additional tools should be exploited to identify the primary tumor. These include immunohistochemistry of transcription factors (CDX-2, Islet-1, TTF-1) [88], PET/CT (e.g. ^{68}Ga -SR, ^{11}C -5-hydroxytryptophan or ^{18}F -DOPA) [89, 90] and upper and lower gastrointestinal endoscopy and optionally capsule endoscopy [91, 92]. If the primary tumor site remains unknown, therapeutic decision making is essentially based on grading, functionality, SSTR status, tumor extent and hepatic tumor burden.

Further information is provided in the consensus guideline updates for other GEP NET [83, 93–97, this issue].

Appendix

All Other Vienna Consensus Conference Participants

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