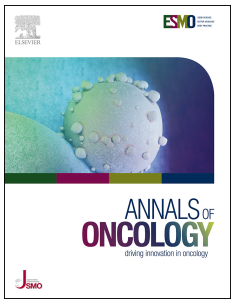

Gastroenteropancreatic neuroendocrine neoplasms: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

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PII: S0923-7534(20)36394-8

DOI: https://doi.org/10.1016/j.annonc.2020.03.304

Reference: ANNONC 145

To appear in: *Annals of Oncology*

Received Date: 19 December 2019

Revised Date: 25 March 2020

Accepted Date: 26 March 2020

Please cite this article as: Pavel M, Öberg K, Falconi M, Krenning E, Sundin A, Perren A, Berruti A, on behalf of the ESMO Guidelines Committee, Gastroenteropancreatic neuroendocrine neoplasms: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†, *Annals of Oncology* (2020), doi: https://doi.org/10.1016/j.annonc.2020.03.304.

Gastroenteropancreatic neuroendocrine neoplasms: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

M. Pavel[1], K. Öberg[2], M. Falconi[3], E. Krenning[4], A. Sundin[5], A. Perren[6] & A. Berruti[7] on behalf of the ESMO Guidelines Committee*

[1]Department of Medicine 1, University Hospital Erlangen, Erlangen, Germany; [2]Department of Endocrine Oncology, Uppsala University, Uppsala, Sweden; [3]Department of Surgery, IRCCS San Raffaele Scientific Institute, Milan, Italy; [4]Cyclotron Rotterdam BV, Erasmus Medical Centre, Rotterdam, The Netherlands; [5]Department of Surgical Sciences, Uppsala University, Uppsala, Sweden; [6]Institute of Pathology, University of Bern, Bern, Switzerland; [7] Department of Medical and Surgical Specialties, Radiological Sciences and Public Health, Medical Oncology Unit, University of Brescia, ASST Spedali Civili, Brescia, Italy.

*Correspondence to: ESMO Guidelines Committee, ESMO Head Office, Via Ginevra 4, CH-6900 Lugano, Switzerland. E-mail: clinicalguidelines@esmo.org

†Approved by the ESMO Guidelines Committee: August 2007, last update March 2020. This publication supersedes the previously published version—Ann Oncol 2012; 23(Suppl 7): vii124–vii130.

Running header: ESMO Clinical Practice Guidelines Gastroenteropancreatic neuroendocrine neoplasms

Word count: 11 856 (excluding headings, funding, acknowledgements); Tables: 3; Figures: 4; Supplementary material: 1; Supplementary Tables: 5

Key words: Gastroenteropancreatic neuroendocrine neoplasms, GEP-NENs, GEP-NETs, Pan-NENs, SI-NETs, Clinical Practice Guidelines, diagnosis, treatment and follow-up

Highlights:

- This ESMO Clinical Practice Guideline provides key recommendations on the management of GEP-NENs
- Authorship includes a multidisciplinary group of experts from different institutions and countries in Europe
- A summary of recommendations is provided, including levels of evidence and grades of recommendation where applicable

Introduction

Neuroendocrine neoplasms (NENs) arise from the diffuse neuroendocrine cell system and may occur at many different disease sites. Most frequently, these neoplasms occur in the digestive system, followed by the lung. The term NEN encompasses well-differentiated neuroendocrine tumours (NETs) and poorly differentiated neuroendocrine carcinomas (NECs). NECs represent only 10%–20% of all NENs. The main focus of these guidelines is on sporadic small intestinal (SI)-NENs and pancreatic NENs (Pan-NENs) since these are the most prevalent NENs at advanced disease stages. In general, the management of other gastrointestinal NENs follows the same principles as in SI- or Pan-NENs taking into consideration key features of NENs such as proliferative activity, somatostatin receptor (SSTR) expression, tumour growth rate and extent of the disease.

Recommendation:

- Diagnostic and therapeutic decision making should be based on key features of NENs such as proliferative activity, SSTR expression, tumour growth rate and extent of the disease [IV, A].

Incidence and epidemiology

Gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) constitute a heterogeneous group of malignancies with a neuronal phenotype and the capacity to secrete amines and hormones. They share similarities with neuroendocrine cells of the embryological gut. The incidence of GEP-NENs has increased more than six-fold between 1997 and 2012 [1].The incidence of localised and regional NENs has increased more than that of NENs with distant metastasis [1]. The incidence of gastroenteropancreatic neuroendocrine tumours (GEP-NETs) in the United States based on an update of the Surveillance, Epidemiology and End Results (SEER) database is estimated to be 3.56/100 000/year. The 20-year limited-duration prevalence has recently been calculated to 48/100 000 [1]. For incidences of individual organs, see supplementary Table S1 available at *Annals of Oncology* online. In Europe, the incidence of GEP-NETs has also increased, and ranges between 1.33–2.33/100 000 population; however, data arise from the national and regional registries and are heterogeneous and mostly retrospective [2-4].

Men are affected slightly more frequently than women and show an adverse outcome. Most NENs are well-differentiated NETs and occur sporadically. GEP-NETs of the pancreas, duodenum, stomach and, more rarely, NETs of the thymus and lung may also arise in the setting of the multiple endocrine neoplasia type 1 (MEN1) syndrome. Pancreatic neuroendocrine tumours (Pan-NETs) are also associated with von Hippel-Lindau (VHL) disease, tuberous sclerosis (TSC) and neurofibromatosis. In these hereditary settings, NETs are multifocal, and the onset of disease is one to two decades earlier than in sporadic tumours. Furthermore, they are often early stage at the time of diagnosis. The frequency of a hereditary background (MEN1, VHL syndromes) was reported as 5% [5]. Recently, whole genomic sequencing revealed 17% of apparently sporadic Pan-NETs carried germline mutations also including DNA repair genes (e.g. *MUTYH, CHEK2, BRCA2*) [6].

Recommendations:

- While most NENs are sporadic, a hereditary background should be considered, particularly in Pan-NETs.

- Genetic testing should be carried out in patients with multiple endocrine neoplasias (hyperparathyroidism and/or pituitary tumours), a family history of NENs or associated diseases and features suspicious of a hereditary disease, as well as in young patients (<40 years) with gastrinoma [IV, A].

Diagnosis and pathology/molecular biology

Histological diagnosis is mandatory in all patients and can be carried out on resection specimens or core biopsies in advanced disease. The diagnosis of a NEN is suspected on haematoxylin eosin (HE)-stained tissue by histomorphological growth pattern and cytology. The neuroendocrine phenotype is proven by the immunohistochemical detection of the neuroendocrine markers synaptophysin and/or chromogranin A (CgA) [III, A]. Absence of both markers is very exceptional in a subset of poorly differentiated NECs, but in this case, other tumour entities must be carefully excluded. Neuron-specific enolase (NSE) and CD56 markers are often positive in GEP-NENs, but are not recommended due to their lack of specificity [7]. GEP-NENs should be classified based on morphology and proliferation (and, rarely, mutation spectrum) into well-differentiated NETs (G1 to G3) and poorly-differentiated NECs (always G3) (Table 1). These two classes of NENs reflect biologically and genetically two different diseases. When showing a high proliferation rate (>20%), there are clear prognostic differences between the two classes. Therefore, the World Health Organization (WHO) 2017 and 2019 classifications split the heterogeneous G3 GEP-NENs into well-differentiated NET G3 and poorly-differentiated NEC G3 [8, 9]. Clinical history, histomorphology and genetics (*DAXX/ATRX/MEN1* mutation in Pan-NET G3, *p53* mutation or *RB* loss in NEC G3) help in separating the groups (Table 2) [8]. The separation of well-differentiated NET G3 from NEC, which had been valid exclusively for Pan-NENs, has now been adopted for gastrointestinal (GI) NENs in an update of the WHO classification for GI NENs [9]. Specific staining for peptide hormones such as gastrin, insulin, glucagon and amines (serotonin) can be applied to confirm the source of a clinical symptomatology, but there is no complete agreement between immunohistochemistry (IHC) and symptomatology, as there can be synthesis of bioactive compounds without secretion [non-functioning (NF)-NENs].

IHC for Ki-67 (MIB1) is mandatory to grade the NENs according to the WHO 2017 and 2019 classifications. Both the number of mitotic figures per 2 mm^2 as well as the Ki-67 index based on assessment of 2000 cells should be reported (Table 1). In the case of a discordant grade between these two methods, the higher grade must be attributed [8]. Other biomarkers are optional, such as SSTR-2 staining, in case functional imaging is not available or *DAXX/ATRX* and *p53/RB* mutations for discrimination of NET G3 and NEC G3 (Table 2) [8]. For appropriate pathological diagnosis, morphology, grading and immunohistochemical staining for CgA and synaptophysin should be reported [III, A].

NETs arising at different anatomical sites of the digestive system represent tumour entities that differ in their biology and clinical presentation (Table 3). Rarely, Pan-NETs may secrete multiple hormones or NETs may transition from NF to functional status [10].

Recommendation:

- For appropriate pathological diagnosis, morphology, grading and immunohistochemical staining for CgA and synaptophysin should be reported. SSTR staining or specific staining for peptide hormones and amines as well as use of molecular markers is optional and dependent on clinical requirements [III, A].

Staging and risk assessment

Disease stage and tumour grade are the two major independent prognostic parameters and should always be assessed [III, A]. Since the WHO 2010 classification, NENs are graded according to Ki-67 index and mitotic count (Table 1). For staging, the tumour, node and metastasis (TNM) staging system proposed by the European Neuroendocrine Tumour Society (ENETS) was recently widely adopted by the eighth edition of the Union for International Cancer Control/American Joint Committee on Cancer (UICC/AJCC) staging system [11] for various types of GEP-NETs. For all NECs, the staging system of adenocarcinomas must be applied [11]. Furthermore, the primary tumour site has an impact on the prognosis in advanced disease.

Patients with Pan-NETs or colorectal NETs have a less favourable prognosis than patients with small intestinal neuroendocrine tumours (SI-NETs) (see supplementary Tables S1, S2, S3 available at *Annals of Oncology* online).

Computed tomography (CT) constitutes the basic radiological method for NET imaging because of its wide availability, standardised reproducible technique and generally high diagnostic yield [12]. Small metastatic lymph nodes (<1 cm) may escape detection by CT. For bone metastases, CT sensitivity is poor at 61% (range 46%–80%). Small peritoneal metastases may be difficult to visualise [13]. The sensitivity of CT to detect NETs is 61%–93% and the specificity is 71%–100% [12, 14, 15]. The detection rate for liver metastases (LMs) is 79% (73%–94%) [16, 17], and for extra-abdominal soft tissue metastases, the sensitivity is 70% (60%–100%) and specificity 96% (range 87%– 100%) [18]. Magnetic resonance imaging (MRI) is advantageous for examination of the liver and the pancreas and is usually preferred in the initial staging and for the preoperative imaging work-up [III, A]. Currently, diffusion-weighted imaging (DWI) with MRI (DW-MRI), which is based on the restricted movement of water in highly cellular tissues such as in tumours, is routinely applied and facilitates lesion detection. The MRI sensitivity to detect Pan NETs is 79% (54%–100%), with fairly similar detection rates of 76% (61%–95%) [19-21], and for LMs, the sensitivity is 75% (range 70%–80%) with near maximum specificity of 98%. The mean sensitivity of MRI for detection of LMs is 91% (range 82%–98%) as compared with CT with a mean sensitivity of 83% (range 75%–98%) [22-26]. MRI is also superior to CT for imaging of the bones and the brain. MRI may, however, miss small lung metastases, and CT is preferred for imaging of the lungs as it offers a better spatial resolution [12]. Contrast-enhanced ultrasound (CEUS) is an excellent method to characterise liver lesions that remain equivocal on CT/MRI. When therapy monitoring is mainly conducted by CT a three-phase CT should be performed. Endoscopic ultrasound (EUS) is the current optimal imaging method to diagnose small Pan-NETs with 86% (range 82%– 93%) sensitivity and 92% (range 86%–95%) specificity [27] and allows also for biopsy, using fine needle aspiration for cytology or, better yet, a cutting needle for histopathological diagnosis. Intraoperative ultrasound (US) facilitates lesion detection/localisation in the pancreas and liver and is mandatory before pancreatic resection in MEN1 syndrome patients.

SSTR imaging by $^{68}Ga/^{18}F/^{64}Cu$ DOTA-somatostatin analogue (SSA) positron emission tomography (PET) in combination with CT (PET-CT) provides high sensitivity for imaging of most types of NET lesions and should be part of the tumour staging, preoperative imaging and restaging [IV, A] [12]. SSTR scintigraphy (SRS) should be carried out when PET-CT is not available but is considerably less sensitive [IV, B]. SRS should include cross-sectional imaging by single photon emission CT (SPECT) together with CT (SPECT-CT). The strength of a PET-CT is a higher detection rate of lymph node, bone and peritoneal lesions as well as unknown primary tumours.

The sensitivity to detect NET disease by ^{68}Ga-DOTA-SSA-PET-CT is 92% (range 64%–100%) and specificity 95% (range 83%–100%) [28]. The sensitivity to detect pancreatic and duodenal NETs is 92% and the specificity 83% [28], and the corresponding values for bone metastases are 97%–100% and 92%–100% [28]. The use of PET with [^{18}F]fluoro-deoxy-glucose (FDG) is optional in NENs. FDG is the tracer of choice for G3 and high G2 NETs, which generally have higher glucose metabolism and less SSTR expression than the low-grade NETs, for which the situation is usually the reverse [29]. Combined SSTR imaging and FDG-PET-CT has been shown to be complementary for lesion detection. Findings of FDG-positive NETs at PET-CT indicate worse prognosis [29-31].

The author panel believes that optimal diagnostic and prognostic information can be achieved by submitting all NET G2/G3 patients to PET-CT with both FDG and ^{68}Ga-DOTA-SSA (DOTATOC/DOTATATE/DOTANOC); however, this procedure needs validation and cannot be generally recommended, but should rather be adopted on an individual basis balancing the potential advantages with the increasing costs [IV, C].

Recommendations:

- Disease stage by TNM classification and tumour grade are the two major independent prognostic parameters and should always be assessed [III, A].
- Whole-body SSTR imaging should be part of the tumour staging, preoperative imaging and restaging [IV, A].
    - $^{68}Ga/^{18}F/^{64}Cu$ SSTR-PET-CT is recommended but, if not available, SRS can be used, although it is considerably less sensitive [IV, B].

  - SRS should include cross-sectional imaging by SPECT.
- MRI should be preferred compared with CT for the detection of LMs, while CT is preferred for imaging of the lungs [III, A].
- The use of FDG-PET is optional in NENs and should be adopted on an individual basis, balancing the potential advantages with the costs [IV, C].

Management of local/locoregional disease

Surgery is the treatment of choice for local or locoregional disease in NET G1 and G2. In functional NETs, clinical symptoms should be managed before any intervention [IV, A].

Pan-NETs

Preoperative evaluation of localised Pan-NETs should take into account tumour size, the presence of unspecific symptoms, functional activity, localisation of the lesion and signs of local invasiveness (Figure 1).

Several studies demonstrated the safety of a watch-and-wait strategy instead of surgery for asymptomatic NF-Pan-NETs ≤2 cm [32, 33]. Nevertheless, the shortness of follow-up and the absence of prospective studies still suggest a cautious attitude towards this approach. Currently, a conservative management of incidentally discovered Pan-NETs ≤2 cm, consisting of a yearly high-quality imaging, is suggested for elderly patients, in the presence of important comorbidities and when a deep localisation in the head of the pancreas allows only a pancreaticoduodenectomy [IV, B] [33]. Surgery is recommended for young patients and in cases when signs of local invasiveness (e.g. dilation of the main pancreatic duct and/or presence of jaundice and/or suspicion of nodal involvement) are present. In the latter condition, a standard pancreatectomy with lymphadenectomy is mandatory, whereas a parenchyma sparing resection (e.g. enucleation or central pancreatectomy) should be routinely considered when the indication for surgery is related to long-life expectancy. Moreover, surgery is mandatory in the presence of functioning Pan-NETs irrespective

of tumour size. Curative resection of localised Pan-NETs seems generally associated with an improved long-term survival and a low risk of recurrence [34]. A standard pancreatectomy (pancreaticoduodenectomy or distal pancreatectomy) with regional lymphadenectomy [35] is recommended for Pan-NETs >2 cm [IV, A]. Enucleation may represent an alternative approach to standard pancreatectomy in selected cases [36]. Functioning Pan-NETs ≤2 cm (e.g. insulinomas) represent ideal lesions to be enucleated, given that they are safely distant from the main pancreatic duct. The role of enucleation for NF-Pan-NETs is currently limited to selected patients with small lesions in whom a watch-and-wait management is contraindicated.

Surgery may also play a role in the presence of borderline or locally advanced Pan-NETs. Pancreatectomy with vascular resection is associated with improved outcomes and it should be carefully considered in the presence of portal and/or superior mesenteric vein invasion. The presence of other high-risk features (e.g. large tumour size and/or high-grade Pan-NEC G3) should discourage an upfront surgical approach [IV, A]. Despite the lack of evidence, in selected patients with high-risk features, a neoadjuvant treatment may be considered. The role of surgery for localised Pan-NEC G3 is still controversial, as upfront surgery may not have a clear benefit in terms of survival [37].

For pancreatic NETs in patients affected by MEN1 syndrome, see Section 1 of supplementary material available at *Annals of Oncology* online.

SI-NETs

Macroscopic radical resection of localised SI-NETs reduces the risk of intestinal complications (bowel obstruction and ischaemia), is associated with improved outcomes [38] and is recommended along with systematic mesenteric lymphadenectomy [IV, A] (Figure 2). Surgical indication for SI-NETs is influenced by the multifocality of these lesions and by the high likelihood of nodal involvement [39]. During surgery for SI-NETs, an accurate palpation of the entire intestine and a systematic lymphadenectomy (at least 8 nodes) are mandatory [39, 40]. The frequent presentation at an emergency setting as well as the rarity of the disease increase the risk of an inadequate surgical resection. Surgery is also generally recommended in the presence of locally advanced SI-NETs, as the presence of a large mesenteric

mass can cause acute or chronic intestinal obstruction and/or localised/diffuse intestinal ischaemia [V, B]. In these cases, a macroscopic radical resection of primary SI-NENs and regional lymph nodes can be achieved in ≤80% of cases if carried out by experienced surgeons [40].

Recommendations:

- Surgery is the treatment of choice for local or locoregional disease in NET G1 and G2. Before any intervention, medical treatment is required in functionally active tumours [IV, A].
- For NF-Pan-NETs ≤2 cm, a conservative approach with surveillance consisting of yearly, high-quality imaging is suggested [IV, B].
- For Pan-NETs >2 cm, the risk of nodal metastases is increased, therefore, a standard pancreatectomy (pancreaticoduodenectomy or distal pancreatectomy) with regional lymphadenectomy is recommended [IV, A].
- The presence of high-risk features (e.g. large borderline tumour size and/or high-grade Pan-NEC G3) should discourage an upfront surgical approach [IV, A].
- NF-Pan-NETs in the setting of MEN1 syndrome are often stable or slow growing; therefore, a watch-and-wait management of these tumours can be safely adopted when ≤2 cm in size [IV, A].
- When surgery is indicated, a minimally invasive approach is recommended whenever feasible [IV, B].
- Macroscopic radical resection of localised SI-NETs is recommended along with systematic mesenteric lymphadenectomy [IV, A].
- Surgery is also recommended in the presence of locally advanced SI-NETs, as the presence of large mesenteric mass can cause acute or chronic intestinal obstruction and/or localised/diffuse intestinal ischaemia [V, B].

Management of advanced/metastatic disease

Surgery for metastatic disease

Given the relatively indolent behaviour of a large fraction of GEP-NENs, surgery also plays a role in metastatic disease [41]. A surgical approach is indicated in selected patients affected by stage IV GEP-NETs who have exclusive or predominant liver involvement, after having carefully evaluated the tumour grading, distribution of LMs and primary site [IV, B]. Upfront surgery should be excluded in the presence of extra-abdominal metastases and high-grade GEP-NENs [IV, B] [42]. It seems reasonable to consider the presence of an advanced NEC G3 as an absolute contraindication for surgery [IV, A], whereas NET G3 should not be excluded *a priori*.

Another crucial parameter for considering a surgical approach is the distribution of LMs [43]. Surgical resection should be attempted in the presence of resectable or potentially resectable LMs [43]. A curative resection (R0, R1) of GEP-NETs with LMs is associated with a 5-year overall survival (OS) rate of around 85% [41]. Preselection biases due to better performance status (PS) or less advanced disease are likely to influence this result. GEP-NET LMs are frequently more extensive than those which are identified, even intraoperatively, and a real curative resection is difficult to achieve. The role of palliative resection is controversial when multiple, unresectable LMs are present. Primary site and presence of symptoms are important factors to be considered before planning a possible palliative surgical resection.

Palliative resection of primary SI-NETs in advanced disease is generally indicated for preventing complications related to bowel obstruction or intestinal ischaemia [IV, C]. However, it is controversial if primary tumour removal in patients with stage IV disease translates to an improvement in survival. A recent large single-centre experience demonstrated no survival benefit in patients with stage IV disease after prophylactic palliative SI-NET resection, compared with no or delayed resection when needed [44].

The role of debulking surgery in advanced NF-GEP-NETs is unclear [38, 41]. Debulking surgery is recommended for alleviating symptoms of the carcinoid syndrome (CS) in patients affected by metastatic functioning SI-NETs [IV, B]. In

those patients with symptoms related to tumour burden, debulking surgery may also be of benefit.

Patients with high tumour burden of functioning Pan-NETs may benefit from debulking surgery [e.g. insulinoma, vasoactive intestinal peptide (VIP)oma], and surgery is generally recommended for this indication [IV, B]. The need for palliative resection of NF-Pan-NETs is debated, as the risk of tumour-related symptoms is low and is not considered in patients with Ki-67 >10% [IV, B]. Despite this, recent evidence from retrospective series suggested that primary Pan-NET resection is associated with better long-term outcomes [45].

Nevertheless, the potential advantage of palliative surgery, either primary tumour resection or debulking surgery in advanced GEP-NETs is controversial in terms of survival and underlies the bias of preselection of better prognosis patients for surgery.

Liver transplantation (LT) may be a valid option in very selected patients with unresectable LMs when the following criteria are met: absence of extrahepatic disease, histological confirmation of a well-differentiated (G1/G2, Ki-67 <10%) NET, previous removal of primary tumour, metastatic diffusion <50% of the total liver volume, stable disease in response to therapy for at least 6 months prior to transplant consideration and age <60 years [IV, B] [20]. In these selected patients with good baseline prognostic factors, a 5-year OS of 69%–97.2% has been reported [46]. LT is preferably considered in patients with functioning tumours (CS refractory to systemic therapies due to high liver tumour burden and in those affected by SI-NETs who usually exhibit a more favourable prognosis). LT should be thoroughly discussed within a NET-dedicated multidisciplinary team, carefully considering all the alternative therapeutic options.

In patients with LMs who are ineligible for complete surgical resection, vascular and ablative locoregional modalities can be considered as an alternative to surgery. Locoregional therapies are discussed in detail in Section 2 of supplementary material available at *Annals of Oncology* online. Locoregional treatments can also be considered as alternative therapy to LM resection in patients with resectable LMs [V, C] combining resection and radiofrequency ablation (RFA) may provide the opportunity to achieve complete tumour removal, allowing more limited resections

when otherwise more extensive hepatectomies could compromise residual liver function.

Adjuvant therapy

There are no data to support adjuvant therapy in NET G1/G2, as data from prospective randomised clinical trials (RCTs) are lacking [IV, A]. However, in aggressive NENs (NEC G3), adjuvant therapy with platinum-based ChT can be considered [V, C]. Prospective clinical trials are warranted.

Medical therapy

The goal of systemic therapy is to control the tumour-associated clinical symptoms and the tumour growth [I, A].

Treatment for symptom control

The use of SSAs (octreotide, lanreotide) is standard first-line therapy in functioning NETs [47]. Improvement of flushing and diarrhoea is achieved in 70%–80% of patients by using slow-release formulations [I, A]. SSAs are in general well-tolerated except for mostly transient GI side effects (diarrhoea, abdominal discomfort, flatulence, nausea). In case of radiological stable disease or slow growth and worsening CS, it is common practice to increase the SSA dose to greater than the standard dose [octreotide long-acting release (LAR) 30 mg intramuscular (i.m.) once every 4 weeks (q4w), lanreotide autogel (AG) 120 mg subcutaneous (s.c.) q4w] by shortening the injection interval to 3 or even 2 weeks of long-acting SSAs to alleviate symptoms [48] although sufficient prospective data are lacking to support this approach [IV, C]. Rescue s.c. octreotide injections are used alternatively, particularly in cases of intermittently increased symptoms. Pasireotide LAR, a universal ligand to SSTR, may be considered off-label based on its efficacy in subsets of patients with CS when established options failed [49]. Furthermore, interferon alpha (IFNα) is approved for symptom control (3–5 million IU s.c. three times weekly) with similar efficacy compared with SSA, but it is usually used in second-line as an add-on treatment to SSA in patients with refractory

syndrome, due to its less favourable toxicity profile (fatigue, weight loss and, more rarely, depression) [II, B] [50].

Telotristat ethyl is an oral inhibitor of tryptophan hydroxylase, a rate-limiting enzyme in the synthesis of serotonin, that has demonstrated a significant improvement in the number of bowel movements in a phase III trial (TELESTAR) with 135 patients with refractory CS diarrhoea (≥4 bowel movements per day) compared with placebo. Durable response (defined as ≥30% improvement in bowel movements for >50% of the 12-week core study period) occurred in 44% and 42% of the patients treated with 250 mg or 500 mg three times a day (tid), respectively [51]. A second placebo-controlled trial (TELECAST) including patients with less frequent bowel movements supports the efficacy and good tolerability of telotristat ethyl. Adverse effects include mild elevations of liver enzymes. Depression-related events and nausea were observed at higher doses [52]. Patients with durable response showed significant and/or meaningful improvements in global quality of life (QoL), as well as nausea, pain, diarrhoea and GI symptoms [53]. Telotristat ethyl (250 mg tid) is approved for treatment of diarrhoea associated with CS in patients insufficiently controlled with SSA and can be recommended for this indication as an add-on treatment to SSA [I, A].

In progressive disease, peptide receptor radionuclide therapy (PRRT) may be considered to improve symptoms [II, B], although efficacy may not be durable (Figure 3) [54, 55]. With regard to the CS in the NETTER-1 study, diarrhoea (present in 48% and 53% in the two treatment arms) improved equally in 48% and in 43% of the patients in the lutetium-177 (^{177}Lu)-DOTATATE + octreotide LAR 30 mg arm versus octreotide LAR 60 mg arm, respectively; however, the time to deterioration (TDD) in QoL for diarrhoea after PRRT is significantly better than the TTD in the control arm. There was no difference in control of other symptoms including flushing [55]. Noteworthy, acute aggravation of symptoms may occur during or after PRRT (such as worsening of hypoglycaemia in insulinoma or diarrhoea in CS) and requires careful observation [IV, A]. More data are needed to best select treatment options in refractory CS, either dose escalation of SSA or add-on of another treatment (e.g. telotristat ethyl, IFNα, PRRT).

Other treatment options for uncontrolled symptoms include everolimus, particularly in metastatic insulinoma, but also refractory CS with progressive disease, although it is not approved in this indication by either the European Medicines Agency (EMA) or the Food and Drug Association (FDA) [IV, B]. Diazoxide is of value in metastatic insulinoma, as it inhibits the secretion of insulin by tumour cells; SSA should be used under surveillance for the risk of worsening hypoglycaemia. Metastatic gastrinoma may be well-controlled with proton pump inhibitors (PPIs) alone over the long term; in uncontrolled Zollinger-Ellison syndrome, SSAs may be used [56]. SSAs are a standard of care in patients with other functioning Pan-NETs such as NET-secreting VIP, glucagon and other bioactive compounds (Table 3). PRRT is an effective treatment for symptom control in functional pancreatic NET refractory to SSA [57].

Antiproliferative treatment

Predictive factors for therapy selection are lacking. The choice of antiproliferative treatment is based on pathological and clinical features, tumour extent, growth behaviour and SSA imaging. Furthermore, the sequential use of drugs is impacted by the evidence level of drug activity, patient comorbidities and accessibility to drugs in different countries.

Antiproliferative medical treatment options include targeted drugs and systemic ChT. SSAs and IFN (also named biotherapy) are the oldest targeted drugs used in NETs while novel targeted drugs, such as the mammalian target of rapamycin (mTOR) inhibitor everolimus and the multiple tyrosine kinase inhibitor (TKI) sunitinib, have been introduced more recently in the management of NETs. None of the available treatment options provides a cure, but rather disease stabilisation with variable duration, depending on different prognostic factors including grade, tumour extent and slope of progression.

Somatostatin analogues

SSAs are an established antiproliferative therapy in metastatic GEP-NETs, based on two placebo-controlled trials. Most frequently, they are used in first-line treatment, based on their modest activity and the settings in which they have been studied.

Overall response rates (ORRs) are low (<5%). The PROMID study showed prolongation of time to tumour progression (TTP) in therapy-naive advanced metastatic midgut NETs (mostly G1 and with low tumour burden) by 8.3 months; TTP with octreotide LAR 30 mg was 14.3 months and 6 months with placebo [58].

The CLARINET study demonstrated efficacy not only in midgut but also in Pan-NETs and NETs with high liver tumour burden (>25%), and NET G2 with a Ki-67 of ≤10%. Most patients (96%) had stable disease at study onset. The median progression-free survival (PFS) was not reached with lanreotide (>27 months) and was 18 months in the placebo arm [59]. The CLARINET extension study also showed efficacy in progressive disease patients with enteropancreatic NETs [60]. There is very good long-term tolerability of both SSAs [47, 58, 59]. SSAs can be recommended for tumour growth control in advanced SSTR-positive, slowly-growing GI and Pan-NETs up to a Ki-67 of 10% [I, A; European Society for Medical Oncology-Magnitude of Clinical Benefit Scale (ESMO-MCBS) v1.1 score: 3] for lanreotide and [I, A; ESMO-MCBS v1.1 score: 2] for octreotide. SSAs can be recommended in patients with unknown disease status, stable or progressive disease. Tumour burden may impact the treatment onset. Positive SSTR status is generally required but is not predictive of response and SSTR imaging, particularly SRS may miss small lesions of <1 cm in size. Since OS benefit is lacking in both SSA trials (CLARINET OS data are still premature), probably due to high crossover rates [59, 61], and patients with indolent tumour behaviour may have stable disease for long time, a watch-and-wait strategy may be applied, particularly in patients with NET G1 and/or low tumour burden (<10% liver tumour burden and absence of extra-abdominal disease) and stable disease [IV, A]. A watch-and-wait approach is less frequently applied in advanced Pan-NETs, the majority of the patients have NET G2 rather than NET G1.

IFNα

Based on long-term experience in NETs [50] and supported by recent results from a large randomized trial (including 35% midgut NET, median PFS 15.4 months for IFNα and octreotide LAR) [62], IFNα can be considered for antiproliferative therapy if other treatment options have been exploited or are not feasible (e.g. SSTR-negative status

on functional imaging), particularly in midgut NETs, where there are fewer options as compared with Pan-NETs [IV, B].

Everolimus

Everolimus has been studied extensively at a dose of 10 mg per day in various subtypes of NENs and has shown activity in Pan-, GI and pulmonary NETs. ORRs are low (<10%) with everolimus. Three prospective studies demonstrate a high disease control rate with everolimus in Pan-NETs. Median PFS ranges between 9.7 months in heavily pre-treated patients (RADIANT-1 study) to 16.6 months in patients with few prior therapies [63, 64].

The registration trial (RADIANT-3 study) with 410 patients (including 40% therapy-naive patients) showed prolongation of PFS by 6 months in advanced progressive Pan-NETs; median PFS was 11 months with everolimus and 5.4 months with placebo [65]. There was a trend toward OS benefit [66]. Everolimus is recommended in progressive Pan-NET G1/G2 with or without prior ChT [I, A; ESMO-MCBS v1.1 score: 3]. Addition of the SSA pasireotide to everolimus did not provide a more durable benefit compared with everolimus alone in progressive Pan-NETs (COOPERATE-2 study) [64]; thus, combination therapy of SSA and everolimus is not recommended [II, D]; exceptions may be functioning Pan-NETs. The positioning of everolimus in the treatment algorithm for progressive Pan-NETs is further studied in comparison with PRRT (COMPETE) and streptozotocin-based ChT (SEQTOR) in ongoing clinical trials (NCT03049189, NCT02246127).

The efficacy of everolimus in advanced NF-GI NETs with poor prognosis has been demonstrated by the RADIANT-4 trial [67]. In this trial, 302 patients with GI and lung NETs were included. Median PFS was 11 months with everolimus and 3.9 months with placebo ([hazard ratio (HR) 0.48]. There was a benefit in terms of PFS prolongation in the GI subgroup [HR 0.56 (0.37–0.8)] and the lung NET subgroup ([HR 0.5 (0.28–0.88)], and everolimus is EMA-approved for NF-GI and lung NETs and patients with clearly progressive GI NETs [I, A; ESMO-MCBS v1.1 score: 3]. The efficacy derived from a *post hoc* analysis revealed heterogeneous response patterns among GI NETs with limited benefit in indolent ileum NET [68]. The author panel recommends the use of everolimus after PRRT in SI-NETs, when PRRT is available [V, A]. However, the

treatment sequence needs to be further studied in the absence of definite predictors of response. Health-related QoL evaluation in the overall study population, as measured by the Functional Assessment of Cancer Therapy-General Questionnaire (FACT-G) did not identify statistically significant improvement with everolimus as compared with placebo [69, 70].

The use of everolimus is less clear in patients with advanced NETs (carcinoids) associated with the CS. Although a prolongation of PFS had been shown with everolimus in combination with octreotide compared with placebo and octreotide, the result was not statistically significant (by central reading) and everolimus is not registered for patients with functioning NETs [71]; nevertheless, clinically beneficial effects have been reported in CS patients. Of note, the final OS results from the RADIANT-2 trial indicate a trend toward unfavourable OS in the everolimus arm, although not statistically different from the placebo arm. Everolimus should be used with caution if considered for patients with CS [72].

Most frequent and relevant side effects include stomatitis (>60%), diarrhoea (~30%), fatigue (~30%), infections (20%–29%), pneumonitis (12%–16%) and hyperglycaemia (10%–13%). A referral to the summary of product characteristics is recommended [73]. Across all randomised everolimus trials, drug-related adverse events were mostly manageable. However, around 60% required dose reduction or treatment interruption [65, 67, 71]. Life-threatening side effects may occur in individual patients (e.g. serious infections, sepsis, thromboembolic events) and require comprehensive patient education and regular careful follow-up investigations while patients are on everolimus treatment.

There are no data to support the use of everolimus in NECs. However, small retrospective studies indicate some value in Pan-NET G3 [74]. Prospective phase II trials are ongoing to assess the activity of everolimus in NET G3 and NECs (NCT02113800, NCT02248012).

Sunitinib

Sunitinib is the only multiple TKI that is EMA-approved in Pan-NETs [I, A; ESMO-MCBS v1.1 score: 3]. In a randomised trial, sunitinib (37.5 mg/day) was compared with

placebo in 171 patients with advanced unresectable Pan-NETs. A significant longer PFS (11.0 versus 5.5 months) was noticed in favour of sunitinib [I, A] [75]. ORR was <10%; there was a trend toward an OS benefit with sunitinib [76]. While treatment was associated with modest side effects, there was no significant improvement in multiple QoL domains, but worsening of diarrhoea with sunitinib versus placebo [77]. Most frequent side effects include diarrhoea (59%), nausea (45%), asthenia (34%), vomiting (34%) and fatigue (32%). Other side effects include hypertension (26%), lymphopaenia (26%) and hair colour changes (29%); referral to the summary of product characteristics is recommended [78]. Results of a phase IV trial confirm the efficacy and safety of sunitinib in patients with advanced, well-differentiated Pan-NETs who were treatment-naive or previously treated with other drugs [79]. Sunitinib is recommended in the management of advanced progressive Pan-NETs [I, A]. The drug has no indication in Pan-NECs due to the lack of data. Promising data from a small phase II study in patients with NET G3 and NEC [80] need to be validated in a larger study.

The appropriate sequencing of targeted drugs remains unclear and is mostly dependent on patient individual factors including comorbidities and side effects of targeted drugs. There are no data to support the use of TKIs outside of clinical trials in GI NETs. However, recent data from a phase III placebo controlled trial (SANET-ep) indicated activity of surufatinib in extra-Pan-NETs in a Chinese population; surufatinib prolonged PFS by 5.4 months compared with placebo in poor prognosis patients (>80% NET G2, most frequent primary sites include the rectum and lung) [81].

Ongoing randomised controlled trials will provide more data on TKIs in the future (see Section 3 of supplementary material available at *Annals of Oncology* online).

Systemic ChT

The use of systemic ChT is recommended in advanced Pan-NETs and in NEN G3 of any site [II, A]. Results with systemic ChT for advanced well-differentiated non-pancreatic NETs of the GI tract are poor; in a systematic review of patients with locally advanced or metastatic well-differentiated G1/G2 GI NETs, the ORR was 11.5% (range 5.8%–17.2%) [82]; thus, ChT cannot be recommended in this setting [II, C]. Preselection of patients with higher probability of response (e.g. higher Ki-67 in

the range of 15%–20%; significant progression) might be associated with benefit from ChT. Systemic ChT may be considered under these conditions in individual cases [V, C] (Figure 4).

Systemic ChT is indicated in patients with non-resectable LMs and/or other distant metastases from G1/G2 Pan-NETs using a combination of streptozotocin (STZ) and 5-fluorouracil (5-FU) [II, A]. ORRs range between 35% and 40%. STZ-based ChT can be considered upfront in bulky disease without documented prior tumour progression. Recent retrospective analyses from European centres support the efficacy demonstrated in RCTs carried out a long time ago [83-85]. From retrospective trials, temozolomide (TEM)-based ChT is active in Pan-NETs, either alone or combined with capecitabine (CAP) [86]; preliminary results from the prospective explorative two-arm phase II trial of CAPTEM in patients (n=145) with progressive Pan-NETs confirm the efficacy of TEM-based ChT and suggest superiority of the combination therapy (CAPTEM) compared with TEM alone with respect to PFS prolongation (22.7 months versus 14.4 months, respectively; HR 0.58, *P*=0.023) [II, B] [87]. However, unbalanced low-grade NETs and a longer time since diagnosis to therapy in favour of the combination arm may have impacted the results. ORRs were not different with TEM (27.8%) versus CAPTEM (33.3%). The value of using O(6)-methylguanine-DNA methyltransferase (MGMT) expression or promoter methylation for preselection of patients is controversial [86, 88].

In cases of liver and/or other distant metastases from high-grade small or large cell NEC G3 regardless of the primary tumour origin combination ChT, using cisplatin/etoposide or carboplatin/etoposide is recommended [III, A]. Although ORRs may be high (30%–67%), median OS (mOS) is very limited (11–19 months). Early treatment onset is crucial for the outcome. There is no established second-line therapy for poorly differentiated NECs, but retrospective studies from single centres indicate some efficacy of TEM alone or in combination with CAP± bevacizumab, of 5-FU intravenously or CAP orally, combined with either oxaliplatin or irinotecan [IV, B] [89, 90].

The ORR with cisplatin-based ChT in NET G3 (in general, Ki-67 is less than 55%) is much lower than in NEC and cisplatin/etoposide is not recommended [IV, C]. Other

options may be considered including TEM, targeted drugs, PRRT in selected cases and STZ-based ChT in the case of Pan-NETs (Figure 4).

PRRT

PRRT is a therapeutic option in progressive SSTR-positive NETs with homogenous SSTR expression (all NET lesions are positive) assessed by SSTR imaging [91, 92]. The two peptides most commonly used for PRRT are DOTATOC and DOTATATE. ^{177}Lu is increasingly preferred to yttrium-90 (^{90}Y)-labelled SSA due its much lower kidney toxicity and the possibility to carry out scintigraphy and thus dosimetry.

Recently, the multicentre prospective phase III NETTER-1 trial has compared ^{177}Lu-DOTATATE (7.4 GBq every 8 weeks, four intravenous infusions) in association with 30 mg octreotide LAR versus 60 mg octreotide LAR alone (every 4 weeks) in 229 patients with metastatic well-differentiated (G1/G2) midgut NETs [93]. Patients had progressive disease within a time frame of up to 3 years, and all had previously been treated with a standard dose of SSA. ^{177}Lu-DOTATATE was superior to high-dose octreotide in terms of PFS (primary end point). Median PFS (mPFS) with ^{177}Lu-DOTATATE was 28.4 months while it was 8.5 months with high-dose octreotide (HR for disease progression 0.214; 95% CI 0.139–0.331) [94]. ^{177}Lu-DOTATATE was also associated with a higher ORR (18% versus 3%) at 3 months after the fourth PRRT cycle. OS analysis is premature and indicates a trend towards OS benefit [93, 94]. Treatment was also associated with an improvement in symptoms and time to QoL deterioration for global health status, physical functioning, fatigue, pain and diarrhoea [55]. PRRT can be recommended in patients with midgut NETs with disease progression on SSAs who fulfil the general requirements for PRRT that are reported elsewhere [I, A] [95]. PRRT can also be considered at further therapy lines and in NETs from other sites than midgut (Figure 4). Several phase II trials and observational studies that recruited more than 1000 patients reported overall ORRs ranging between 4% and 39% in patients with both functioning and NF-SSTR-positive NETs including NETs of the pancreas or GI tract outside the midgut region [54, 96-98]. ^{177}Lu-DOTATATE has been approved by the EMA and the FDA, not only in patients with midgut NETs [I, A; ESMO-MCBS v1.1 score: 4] but also in patients with Pan-NETs [III, A; ESMO-MCBS v1.1 score: 4]. Results from RCTs with PRRT in Pan-

NETs are lacking and molecular targeted agents, such as everolimus or sunitinib, and systemic ChT may therefore be preferred treatment choices, and PRRT after failure of these approved therapies [III, A] (Figure 4). However, one author (EPK) feels that PRRT should be considered earlier in the treatment algorithm for Pan-NETs.

For more information about selection criteria and PRRT biomarkers, see Section 4 of supplementary material available at *Annals of Oncology* online.

The published data on results of PRRT in NEN G3 of about 280 patients in 4 retrospective studies with a number of patients ranging between 28–149 with Ki-67 >20% support the therapeutic consideration of PRRT also in this group of patients [99-102]. The overall results show disease control rates between 30%– 80%, PFS 9–23 months and OS 19–53 months. The results were significantly better in patients with a Ki-67 <55% compared with those with higher Ki-67 values (there are fewer patients with a Ki-67 >55%). In patients with a Ki-67 of >35%, mPFS was 6.8 months in one study [101], and in patient subgroups with Ki-67 >55%, mPFS was 6 months, 4 months and 4 months, respectively from the different studies [99, 100, 102]. PRRT may be considered in patients with NET G3 [IV, C], however, patients need to be carefully selected and prospective trials are warranted to further establish which patients with NEN G3 might benefit most from PRRT. The NETTER-2 trial has recently been initiated to address this issue (NCT03972488).

PRRT safety

Treatment with ^{177}Lu-DOTATATE is in general considered safe, however, up to 3–4% of the patients may develop irreversible bone marrow toxicity such as leukaemia or bone marrow dysplasia. Mild renal toxicity grade 1/2 has been reported long term in 30% of the patients (see Section 5 of supplementary material available at *Annals of Oncology* online).

For more information about PRRT and SSA combination and maintenance therapy, see Section 6 of supplementary material available at *Annals of Oncology* online.

Recommendations:

- A surgical approach is indicated in selected patients affected by stage IV GEP-NETs who show exclusive or predominant liver disease after careful evaluation of tumour grading, distribution of LMs and primary site [IV, B].
- Upfront surgery is not indicated in the presence of extra-abdominal metastases and high-grade GEP-NENs [IV, B].
- Presence of an advanced NEC G3 is considered an absolute contraindication for an upfront surgery [IV, A].
- Palliative resection of primary SI-NETs in advanced disease is generally indicated for preventing complications related to bowel obstruction or intestinal ischaemia [IV, C]. However, it is controversial if primary tumour removal in patients with stage IV disease translates to an improvement in survival.
- Debulking surgery is recommended for alleviating symptoms in patients affected by metastatic functioning SI-NETs [IV, B].
- In advanced Pan-NETs with uncontrolled symptoms related to hormone hypersecretion, debulking surgery may be indicated [IV, B], but is generally not considered in patients with Ki-67 >10% [IV, B].
- LTs may be a valid option in very selected patients with unresectable LMs [IV, B].
- Locoregional treatments can be considered as an alternative therapy to LM resection in patients with resectable LMs [V, C].
- Adjuvant therapy is not indicated in NET G1/G2 [IV, A]. However, in aggressive NENs (NEC G3), adjuvant therapy with platinum-based ChT may be considered [V, C].
- Vascular and ablative locoregional treatments are valid options for treatment of LMs, also in conjunction with other systemic therapies or in combination with surgery. The choice of the procedures depends on the local expertise, the extension and vascularisation of LMs and the localisation of liver involvement [V, C].
- In functional NETs, locoregional therapies should be applied early, following SSA therapy, to further improve control of hormonal symptoms and prevent complications (e.g. carcinoid crisis in serotonin-secreting NETs) [IV, A].

- In patients with NF-NETs with disease limited to the liver, locoregional therapies can be considered as an alternative to systemic treatment [IV, B].
- Systemic therapy should be administered to control tumour-associated clinical symptoms and tumour growth [I, A].
- The use of SSAs is standard first-line therapy in patients with CS and some rare functional Pan-NETs (e.g. VIPoma, glucagonoma) [I, A].
- In patients with refractory diarrhoea related to CS, telotristat ethyl can be recommended as an add-on treatment to SSAs [I, A].
- SSA dose increase is an alternative approach to improve symptoms in refractory CS [IV, C], as well as the use of IFNα, although it is less well-tolerated [II, B].
- In progressive disease, PRRT may have a significant impact on diarrhoea control in patients with CS [II, B].
- Hormonal crisis may occur soon after PRRT and requires careful information to be given to the patient directly after PRRT, and eventually admission and proper treatment [IV, A].
- The choice of antiproliferative treatment is based on pathological and clinical features, tumour extent, growth behaviour and SSA imaging.
- A watch-and-wait strategy may be followed in patients with low Ki-67 (<2%), low tumour burden and stable disease [IV, A], preferably in SI-NETs with long-term favourable prognosis.
- SSAs can be recommended as first-line therapy for tumour growth control in advanced, slowly-growing SSTR-positive GI and Pan-NETs up to a Ki-67 of 10% [I, A; ESMO-MCBS v1.1 score: 3] for lanreotide and [I, A; ESMO-MCBS v1.1 score: 2] for octreotide. Positive SSTR status is generally required but is not predictive of response.
- IFNα can be considered for antiproliferative therapy if other treatment options have been exploited or are not feasible (e.g. SSTR-negative on functional imaging), particularly in midgut NETs, where there are fewer therapy options compared with Pan-NETs [IV, B].

- Everolimus is EMA-approved for progressive Pan-NET G1/G2 with or without prior ChT, for NF-GI and lung NETs and patients with clearly progressive GI NETs [I, A; ESMO-MCBS v1.1 score: 3]. Everolimus is a treatment option in patients with clearly progressive GI NETs [I, A].
- The use of everolimus after PRRT is recommended in intestinal NETs, if PRRT is available [V, A], although the treatment sequence needs to be further studied in the absence of definite predictors of response.
- The combination therapy of SSA and everolimus for an antiproliferative purpose is not recommended [II, D].
- Sunitinib is one of the EMA-approved treatment options in advanced progressive Pan-NETs [I, A; ESMO-MCBS v1.1 score: 3].
- Both sunitinib and everolimus cannot be recommended in NEC G3 outside of clinical trials [V, E].
- The use of systemic ChT is recommended in advanced Pan-NETs and in NEN G3 of any site [II, A].
    - In patients with non-resectable LMs and/or other distant metastases from G1/G2 Pan-NETs, STZ/5-FU is recommended in progressive disease [II, A].
    - TEM alone or in combination with CAP is recommended as alternative ChT in Pan-NETs [II, B].
    - Systemic ChT can also be recommended in bulky disease without prior tumour progression in Pan-NETs [II, B].
    - Cisplatin or carboplatin with etoposide is recommended standard first-line ChT in NEC G3 [III, A]. There is no established second-line therapy, but different regimens [e.g. 5-fluorouracil/leucovorin/irinotecan (FOLFIRI), 5-fluorouracil/leucovorin/oxaliplatin (FOLFOX), CAPTEM +/- bevacizumab] may be considered [IV, B].
- In NET G3, response rates to cisplatin/etoposide are low, and the use of this combination is not recommended [IV, C].

- ChT cannot be recommended in well-differentiated slowly growing NETs of the GI tract [II, C]; exceptions may be rapidly progressive tumours or NET G2 with higher Ki-67 close to NET G3 [V, C].
- PRRT is recommended as second-line therapy in patients with midgut NETs with disease progression on SSAs who fulfil the general requirements for PRRT [I, A].
- ^{177}Lu-DOTATATE is EMA- and FDA-approved for patients with midgut NETs [I, A; ESMO-MCBS v1.1 score: 4] and Pan-NETs [III, A; ESMO-MCBS v1.1 score: 4].
- In Pan-NETs, PRRT should be used after failure of approved therapies [III, A].
- In carefully selected patients, PRRT may be considered in NET G3 [IV, C].
- SSA should be combined with PRRT in patients with functioning tumours (CS) to prevent increasing symptoms such as diarrhoea and/or flushing and hormonal crisis soon after PRRT [II, A].
- It is also common practice to continue SSA beyond PRRT in functioning tumours, as a full resolution of CS related symptoms is rarely achieved after PRRT [II, A].
- The combination of SSA with PRRT is not recommended in patients with NF-NETs, [IV, C] and it remains unclear if SSA should be continued after PRRT as a maintenance therapy.

Personalised medicine

In the absence of definite predictive markers and paucity of comparative randomised trials, therapy selection in advanced non-resectable disease is frequently based on individual patient clinical and pathological features and SSTR imaging [IV, A]. Several issues are unresolved: to consider surgery for potentially resectable LMs or systemic therapy, as well as upfront locoregional therapies in LMs versus systemic treatment. Among systemic treatments, approved drugs should be used with higher priority, although comorbidities and age may impact treatment choices. The treatment selection should be based on an interdisciplinary tumour board decision in

experienced centres including experts familiar with the disease. Recently identified prognostic molecular markers may have an impact on therapy strategies in the future if validated in prospective trials. A recent meta-analysis identified a diagnostic accuracy of a NET mRNA genomic biomarker (NETest) of 95%–96%; this marker seems to have a predictive value for PRRT response and achievement of complete surgery [103].

Recommendation:

- In the absence of definite predictive markers and paucity of comparative randomised trials, therapy selection in advanced disease is often based on individual patient clinical and pathological features and SSTR imaging [IV, A].

Follow-up, long-term implication and survivorship

Follow-up investigations should include clinical symptom monitoring, biochemical parameters and conventional and SSTR imaging [V, B]. In patients with R0/R1-resected NET G1 and NET G2 with low Ki-67 (<5%), it is recommended that imaging is carried out every 6 months (CT or MRI), in NET G2 (Ki-67 >5%) every 3 months and in NEC G3 every 2–3 months [V, C]. Similar staging intervals apply to advanced disease. Follow-up should be life long, although the staging intervals can be extended to 1–2 years with increasing length of follow-up (>5 years), except in G3 NEN, where shorter intervals should be kept. Late recurrences after 10–20 years have been described, although rare. In contrast, small localised NET G1 (<1 cm in size) with origin in the appendix or rectum do not need any follow-up if R0-resected and in the absence of adverse histological features [IV, A].

SSTR imaging with ^{68}Ga/^{18}F/^{64}Cu-DOTATOC/PET-CT, or if not available with SSTR scintigraphy as a considerably less sensitive alternative, should be included in the follow-up and is recommended after 12–36 months if expression of SSTR-2a has been demonstrated on the tumour cells by previous SSTR imaging or IHC [91, 92]. In the follow-up, a re-biopsy of the liver or other disease site (in absence of LMs) may be considered under special circumstances, e.g. if a second malignancy is suspected or the tumour growth behaviour is inconsistent with the known Ki-67 and warrants

exclusion of a NEC. Biochemical markers include CgA and specific biomarkers in functional tumours; if CgA is not elevated, NSE represents an alternative biomarker, mostly in NET G2 or NEN G3. There is no validated tumour marker for recurrence detection; the NETest has potential to predict and detect residual disease after surgery and was superior to CgA in a validation study [104-106].

In NEN G3 clinical symptoms (weight loss, fatigue; also indicative in G1 and G2) may indicate recurrence. NSE and lactate dehydrogenase (LDH) should be monitored in NEC; CgA may also be elevated in NET G3. Conventional imaging includes thoracic and abdominal scans every 2-3 months. FDG-PET may be required in case of suspected recurrence to discriminate lesions from unspecific findings; otherwise, high-resolution CT is the imaging method of choice, unless resection is considered in locally advanced NEN G3, where FDG-PET is mandatory to exclude distant metastatic disease.

Recommendations:

- Follow-up investigations should include clinical symptom monitoring, biochemical parameters and conventional and SSTR imaging [V, B].
- In patients with R0/R1-resected NET G1–G2, it is recommended that imaging is carried out every 6 months (CT or MRI), and in NEC G3 every 2–3 months [V, C]. Similar staging intervals apply to advanced disease.
- Follow-up should be lifelong, although the staging intervals may be extended to 1– 2 years with increasing length of follow-up.
- Small localised NET G1 (<1 cm in size) with origin in the appendix or rectum do not need any follow-up if R0-resected and in the absence of adverse histological features [IV, A].

Methodology

These Clinical Practice Guidelines were developed in accordance with the ESMO standard operating procedures for Clinical Practice Guidelines development, http://www.esmo.org/Guidelines/ESMOGuidelines-Methodology. The relevant literature has been selected by the expert authors. An ESMO-MCBS table with

ESMO-MCBS scores is included in supplementary Table S4 available at *Annals of Oncology* online. Levels of evidence and grades of recommendation have been applied using the system shown in supplementary Table S5 available at *Annals of Oncology* online. Statements without grading were considered justified standard clinical practice by the experts and the ESMO Faculty. This manuscript has been subjected to an anonymous peer review process.

Acknowledgements

The ESMO Guidelines Committee would like to thank the ESMO Faculty and other experts who provided critical reviews of these ESMO Clinical Practice Guidelines. They would also like to thank the European Cancer Patient Coalition and the CarciNor group for their review.

Funding

No external funding has been received for the preparation of these guidelines. Production costs have been covered by ESMO from central funds.

Disclosure

MP received honoraria for advisory board and presentations from Novartis, IPSEN, Pfizer and Lexicon, honoraria for presentations for Prime Oncology and research funding from IPSEN and Novartis. MF received honoraria for presentations from Novartis, IPSEN, Advanced Accelerator Applications (AAA) and Prime Oncology, honoraria for advisory board from AAA and research funding from IPSEN and Novartis; EPK has an employment interest at Cyclotron Rotterdam BV, stock or other interest from AAA, patent or intellectual property interest (AAA) and travel, accommodation or expenses (AAA); AS has received lecture honoraria from Ipsen and honoraria from AAA; AB has received consultation, advisory and paid public speaking from Bayer, Janssen, Astellas and Novartis and research grants from Janssen and Astellas. AP and KÖ have declared no potential conflicts of interest.

Figure 1. Surgical approach in sporadic Pan-NETs

ASA, American Society of Anesthesiologists; NET, neuroendocrine tumour; Pan-NET, pancreatic neuroendocrine tumour; RECIST, Response Evaluation Criteria In Solid Tumours.

→ Indicates progressive disease.

[a]Slow tumour growth is defined as stable disease by RECIST criteria for >1 year. Surgery and/or liver-directed locoregional options may be combined and/or alternative options in patients with liver metastases, where applicable.

[b]To be considered only in exceptional cases (particularly in functioning tumours) in the absence of extrahepatic disease, histological confirmation of a well-differentiated (G1–G2, Ki-67 <10%) NET, previous removal of primary tumour, metastatic diffusion <50% of the total liver volume, stable disease to therapies for at least 6 months before transplant consideration and age <60 years.

Figure 2. Surgical approach in SI-NETs

NET, neuroendocrine tumour; RECIST, Response Evaluation Criteria In Solid Tumours; SI-NET, small intestinal neuroendocrine tumour.

⟶ Indicates progressive disease.

[a]Slow tumour growth is defined as stable disease by RECIST criteria for >1 year. Surgery and/or liver-directed locoregional options may be combined and/or alternative options in patients with liver metastases, where applicable.

[b]To be considered only in exceptional cases (particularly in functioning tumours) in the absence of extrahepatic disease, histological confirmation of a well-differentiated (G1–G2, Ki-67 <10%) NET, previous removal of primary tumour, metastatic diffusion <50% of the total liver volume, stable disease on medical therapies for at least 6 months before transplant consideration and age <60 years.

Figure 3. Therapeutic approach in NETs with carcinoid syndrome

^{177}Lu, lutetium-177; IFNα, interferon alpha; LAR, long-acting release; NET, neuroendocrine tumour; PRRT, peptide receptor radionuclide therapy; RFA, radiofrequency ablation; s.c., subcutaneous; SIRT, selective internal radiotherapy; SSA, somatostatin analogue; SSTR, somatostatin receptor; TACE, transarterial chemoembolisation; TAE, transarterial embolisation; TE, telotristat ethyl.

→ Indicates progressive disease.

[a]SSAs can be tried in SSTR-negative patients, particularly if tumour burden is very low and/or lesion size is very small (potentially false-negative SSTR status).

[b]Long-acting SSAs should be interrupted at least 4 weeks before PRRT and should be continued not earlier than one hour after PRRT cycle(s).

[c]PRRT may be considered in patients without prior tumour progression but with high tumour burden and uncontrolled diarrhoea (off-label).

[d]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.

[e]IFNα should be interrupted if PRRT is considered.

[f]TE can be continued with other treatments if patient has a benefit; it is not an option if patient has predominant flushing.

Figure 4. Systemic therapy in GEP-NENs

5-FU, 5-fluorouracil; CAP, capecitabine; CAPTEM, capecitabine and temozolomide; ChT, chemotherapy; EVE, everolimus; FOLFIRI, 5-fluorouracil/leucovorin/irinotecan; FOLFOX, 5-fluorouracil/leucovorin/oxaliplatin; GEP-NET, gastroenteropancreatic neuroendocrine neoplasm; IFNα, interferon alpha; NEC, neuroendocrine carcinoma; NET, neuroendocrine tumour; ORR, overall response rate; Pan-NET, pancreatic neuroendocrine tumour; PRRT, peptide receptor radionuclide therapy; RECIST, Response Evaluation Criteria In Solid Tumours; SI, small intestinal; SI-NET, small intestinal neuroendocrine tumour; SSA, somatostatin analogue; SSTR, somatostatin receptor; STZ, streptozotocin; SUN, sunitinib; TEM, temozolomide.

The stratification factors are not predictive, but prognostic.

A watch-and-wait approach is recommended in asymptomatic low-grade tumour patients with absence of morphological progression. Locoregional therapy may be considered as an alternative approach to systemic therapies in SI- and Pan-NETs in liver disease only or predominant liver disease if extrahepatic lesions are stable. Locoregional therapy may also be considered early in NET G2 patients and advanced disease.

In Pan-NET G3 with moderate Ki-67, the treatment is similar to Pan-NET G2. The choice of ChT is mainly based on the tumour growth rate and Ki-67. STZ-based and TEM-based therapies provide similar ORRs, although a comparative study is not available.

STZ has been combined with doxorubicin in Pan-NETs and produced high ORRs, but its use is limited due to potential cardiotoxicity to maximal cumulative dose of 400 mg/m^2.

→ Indicates progressive disease.

[a]Slow tumour growth is defined as stable disease by RECIST criteria for >1 year.

[b]In liver-dominant disease.

[c]If PRRT is not available, everolimus can be used as second-line therapy.

[d]Rapid growth is defined as RECIST progression within a year or less.

[e]In liver-only disease or predominant liver disease.

[f]If SSTR-positive.

[g]One author (EPK) indicates that in SSTR positive Pan-NET G1/G2 (Ki-67 <10%) PRRT might be considered after first-line SSA or chemotherapy, equal to the choice of targeted drugs.

References

1. Dasari A, Shen C, Halperin D et al. Trends in the incidence, prevalence and survival outcomes in patients with neuroendocrine tumors in the United States. JAMA Oncol 2017; 3: 1335-1342.

2. Fraenkel M, Kim M, Faggiano A et al. Incidence of gastroenteropancreatic neuroendocrine tumours: a systematic review of the literature. Endocr Relat Cancer 2014; 21: R153-R163.

3. Leoncini E, Boffetta P, Shafir M et al. Increased incidence trend of low-grade and high-grade neuroendocrine neoplasms. Endocrine 2017; 58: 368-379.

4. Huguet I, Grossman AB, O'Toole D. Changes in the epidemiology of neuroendocrine tumours. Neuroendocrinology 2017; 104: 105-111.

5. Rindi G, Falconi M, Klersy C et al. TNM Staging of neoplasms of the endocrine pancreas: results from a large international cohort study. J Natl Cancer Inst 2012; 104: 764-777.

6. Scarpa A, Chang DK, Nones K et al. Whole-genome landscape of pancreatic neuroendocrine tumours. Nature 2017; 543: 65-71.

7. Perren A, Couvelard A, Scoazec JY et al. ENETS Consensus guidelines for the standards of care in neuroendocrine tumors: pathology: diagnosis and prognostic stratification. Neuroendocrinology 2017; 105: 196-200.

8. Kloeppel G. Pancreatic neuroendocrine neoplasias. In The WHO classification of endocrine tumors;. Lyon, France: IARC Press 2017.

9. WHO Classification of Tumours Editorial Board; Digestive System Tumours, WHO Classification of Tumours, 5th Edition. Lyon, France: IARC Press,2019.

10. de Mestier L, Hentic O, Cros J et al. Metachronous hormonal syndromes in patients with pancreatic neuroendocrine tumors: a case-series study. Ann Intern Med 2015; 162: 682-689.

11. Brierley JD, Gospodarowicz MK, Wittekind C. TNM classification of malignant tumours, 8th Edition. Oxford, UK: John Wiley & Sons,2016.

12. Sundin A, Arnold R, Baudin E et al. ENETS Consensus guidelines for the standards of care in neuroendocrine tumors: radiological, nuclear medicine & hybrid imaging. Neuroendocrinology 2017; 105: 212-244.

13. Norlen O, Montan H, Hellman P et al. Preoperative (68)Ga-DOTA-somatostatin analog-PET/CT hybrid imaging increases detection rate of intra-abdominal small Intestinal neuroendocrine tumor lesions. World J Surg 2018; 42: 498-505.

14. Gabriel M, Decristoforo C, Kendler D et al. 68Ga-DOTA-Tyr3-octreotide PET in neuroendocrine tumors: comparison with somatostatin receptor scintigraphy and CT. J Nucl Med 2007; 48: 508-518.

15. Procacci C, Carbognin G, Accordini S et al. Nonfunctioning endocrine tumors of the pancreas: possibilities of spiral CT characterization. Eur Radiol 2001; 11: 1175-1183.

16. Fidler JL, Fletcher JG, Reading CC et al. Preoperative detection of pancreatic insulinomas on multiphasic helical CT. AJR Am J Roentgenol 2003; 181: 775-780.

17. Gouya H, Vignaux O, Augui J et al. CT, endoscopic sonography, and a combined protocol for preoperative evaluation of pancreatic insulinomas. AJR Am J Roentgenol 2003; 181: 987-992.

18. Kim JH, Eun HW, Kim YJ et al. Pancreatic neuroendocrine tumour (PNET): Staging accuracy of MDCT and its diagnostic performance for the differentiation of PNET with uncommon CT findings from pancreatic adenocarcinoma. Eur Radiol 2016; 26: 1338-1347.

19. Putzer D, Gabriel M, Henninger B et al. Bone metastases in patients with neuroendocrine tumor: 68Ga-DOTA-Tyr3-octreotide PET in comparison to CT and bone scintigraphy. J Nucl Med 2009; 50: 1214-1221.

20. Schmid-Tannwald C, Schmid-Tannwald CM, Morelli JN et al. Comparison of abdominal MRI with diffusion-weighted imaging to 68Ga-DOTATATE PET/CT in detection of neuroendocrine tumors of the pancreas. Eur J Nucl Med Mol Imaging 2013; 40: 897-907.

21. Brenner R, Metens T, Bali M et al. Pancreatic neuroendocrine tumor: added value of fusion of T2-weighted imaging and high b-value diffusion-weighted imaging for tumor detection. Eur J Radiol 2012; 81: e746-749.

22. d'Assignies G, Fina P, Bruno O et al. High sensitivity of diffusion-weighted MR imaging for the detection of liver metastases from neuroendocrine tumors: comparison with T2-weighted and dynamic gadolinium-enhanced MR imaging. Radiology 2013; 268: 390-399.

23. Ronot M, Clift AK, Baum RP et al. Morphological and functional imaging for detecting and assessing the resectability of neuroendocrine liver metastases. Neuroendocrinology 2018; 106: 74-88.

24. Dromain C, Baere Td, Lumbroso J et al. Detection of liver metastases from endocrine tumors: a prospective comparison of somatostatin receptor scintigraphy, computed tomography, and magnetic resonance imaging. J Clin Oncol 2005; 23: 70-78.

25. Cwikla JB, Buscombe JR, Caplin ME et al. Diagnostic imaging of carcinoid metastases to the abdomen and pelvis. Med Sci Monit 2004; 10 Suppl 3: 9-16.

26. Chambers AJ, Pasieka JL, Dixon E, Rorstad O. Role of imaging in the preoperative staging of small bowel neuroendocrine tumors. J Am Coll Surg 2010; 211: 620-627.

27. Anderson MA, Carpenter S, Thompson NW et al. Endoscopic ultrasound is highly accurate and directs management in patients with neuroendocrine tumors of the pancreas. Am J Gastroenterol 2000; 95: 2271-2277.

28. Geijer H, Breimer LH. Somatostatin receptor PET/CT in neuroendocrine tumours: update on systematic review and meta-analysis. Eur J Nucl Med Mol Imaging 2013; 40: 1770-1780.

29. Binderup T, Knigge U, Loft A et al. 18F-fluorodeoxyglucose positron emission tomography predicts survival of patients with neuroendocrine tumors. Clin Cancer Res 2010; 16: 978-985.

30. Has Simsek D, Kuyumcu S, Turkmen C et al. Can complementary 68Ga-DOTATATE and 18F-FDG PET/CT establish the missing link between histopathology and therapeutic approach in gastroenteropancreatic neuroendocrine tumors? J Nucl Med 2014; 55: 1811-1817.

31. Naswa N, Sharma P, Gupta SK et al. Dual tracer functional imaging of gastroenteropancreatic neuroendocrine tumors using 68Ga-DOTA-NOC PET-CT and 18F-FDG PET-CT: competitive or complimentary? Clin Nucl Med 2014; 39: e27-34.

32. Partelli S, Cirocchi R, Crippa S et al. Systematic review of active surveillance versus surgical management of asymptomatic small non-functioning pancreatic neuroendocrine neoplasms. Br J Surg 2017; 104: 34-41.

33. Falconi M, Eriksson B, Kaltsas G et al. ENETS Consensus guidelines update for the management of patients with functional pancreatic neuroendocrine tumors and non-functional pancreatic neuroendocrine tumors. Neuroendocrinology 2016; 103: 153-171.

34. Jilesen AP, van Eijck CH, In't Hof KH et al. Postoperative complications, in-hospital mortality and 5-year survival after surgical resection for patients with a pancreatic neuroendocrine tumor: a systematic review. World J Surg 2015; 40.

35. Partelli S, Gaujoux S, Boninsegna L et al. Pattern and clinical predictors of lymph node involvement in nonfunctioning pancreatic neuroendocrine tumors (NF-PanNETs). JAMA Surg 2013; 148: 932-939.

36. Chua TC, Yang TX, Gill AJ, Samra JS. Systematic review and meta-analysis of enucleation versus standardized resection for small pancreatic lesions. Ann Surg Oncol 2016; 23: 592-599.

37. Yoshida T, Hijioka S, Hosoda W et al. Surgery for pancreatic neuroendocrine tumor G3 and carcinoma G3 should be considered separately. Ann Surg Oncol 2019; 26: 1385-1393.

38. Norlen O, Stalberg P, Oberg K et al. Long-term results of surgery for small intestinal neuroendocrine tumors at a tertiary referral center. World J Surg 2012; 36: 1419-1431.

39. Lardiere-Deguelte S, de Mestier L, Appere F et al. Toward a preoperative classification of lymph node metastases in patients with small intestinal neuroendocrine tumors in the era of intestinal-sparing surgery. Neuroendocrinology 2016; 103: 552-559.

40. Pasquer A, Walter T, Hervieu V et al. Surgical management of small bowel neuroendocrine tumors: specific requirements and their impact on staging and prognosis. Ann Surg Oncol 2015; 22 Suppl 3: S742-749.

41. Frilling A, Modlin IM, Kidd M et al. Recommendations for management of patients with neuroendocrine liver metastases. Lancet Oncol 2014; 15: e8-21.

42. Cho CS, Labow DM, Tang L et al. Histologic grade is correlated with outcome after resection of hepatic neuroendocrine neoplasms. Cancer 2008; 113: 126-134.

43. Frilling A, Li J, Malamutmann E et al. Treatment of liver metastases from neuroendocrine tumours in relation to the extent of hepatic disease. Br J Surg 2009; 96: 175-184.

44. Daskalakis K, Karakatsanis A, Hessman O et al. Association of a prophylactic surgical approach to stage IV small intestinal neuroendocrine tumors with survival. JAMA Oncol 2018; 4: 183-189.

45. Partelli S, Cirocchi R, Rancoita PMV et al. A Systematic review and meta-analysis on the role of palliative primary resection for pancreatic neuroendocrine neoplasm with liver metastases. HPB (Oxford) 2018; 20: 197-203.

46. Mazzaferro V, Sposito C, Coppa J et al. The Long-term benefit of liver transplantation for hepatic metastases from neuroendocrine tumors. Am J Transplant 2016; 16: 2892-2902.

47. Modlin IM, Pavel M, Kidd M, Gustafsson BI. Review article: somatostatin analogues in the treatment of gastroenteropancreatic neuroendocrine (carcinoid) tumours. Aliment Pharmacol Ther 2010; 31: 169-188.

48. Broder MS, Beenhouwer D, Strosberg JR et al. Gastrointestinal neuroendocrine tumors treated with high dose octreotide-LAR: a systematic literature review. World J Gastroenterol 2015; 21: 1945-1955.

49. Wolin EM, Jarzab B, Eriksson B et al. Phase III study of pasireotide long-acting release in patients with metastatic neuroendocrine tumors and carcinoid symptoms refractory to available somatostatin analogues. Drug Des Devel Ther 2015; 9: 5075-5086.

50. Oberg K. Interferon in the management of neuroendocrine GEP-tumors: a review. Digestion 2000; 62 Suppl 1: 92-97.

51. Kulke MH, Horsch D, Caplin ME et al. Telotristat Ethyl, a Tryptophan Hydroxylase Inhibitor for the Treatment of Carcinoid Syndrome. J Clin Oncol 2017; 35: 14-23.

52. Pavel M, Gross DJ, Benavent M et al. Telotristat ethyl in carcinoid syndrome: safety and efficacy in the TELECAST phase 3 trial. Endocr Relat Cancer 2018; 25: 309-322.

53. Pavel M, Cella D, Beaumont JL et al. 445PRelationship between symptoms and health-related quality of life benefits in patients with carcinoid syndrome: Post-hoc analyses from TELESTAR. Ann Oncol 2017; 28: v142-157.

54. Bushnell DL, Jr., O'Dorisio TM, O'Dorisio MS et al. 90Y-edotreotide for metastatic carcinoid refractory to octreotide. J Clin Oncol 2010; 28: 1652-1659.

55. Strosberg J, Wolin E, Chasen B et al. Health-related quality of life in patients with progressive midgut neuroendocrine tumors treated with (177)Lu-Dotatate in the phase III NETTER-1 Trial. J Clin Oncol 2018; 36: 2578-2584.

56. Ito T, Lee L, Jensen RT. Treatment of symptomatic neuroendocrine tumor syndromes: recent advances and controversies. Expert Opin Pharmacother 2016; 17: 2191-2205.

57. Zandee WT, Brabander T, Blazevic A et al. Symptomatic and Radiological Response to 177Lu-DOTATATE for the Treatment of Functioning Pancreatic Neuroendocrine Tumors. J Clin Endocrinol Metab 2019; 104: 1336-1344.

58. Rinke A, Muller HH, Schade-Brittinger C 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; 27: 4656-4663.

59. Caplin ME, Pavel M, Cwikla JB et al. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. N Engl J Med 2014; 371: 224-233.

60. Caplin ME, Pavel M, Cwikla JB et al. Anti-tumour effects of lanreotide for pancreatic and intestinal neuroendocrine tumours: the CLARINET open-label extension study. Endocr Relat Cancer 2016; 23: 191-199.

61. Rinke A, Wittenberg M, Schade-Brittinger C 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 (PROMID): Results of long-term survival. Neuroendocrinology 2017; 104: 26-32.

62. Yao JC, Guthrie KA, Moran C et al. Phase III prospective randomized comparison trial of depot octreotide plus interferon alfa-2b versus depot octreotide plus bevacizumab in patients with advanced carcinoid tumors: SWOG S0518. J Clin Oncol 2017; 35: 1695-1703.

63. Yao JC, Lombard-Bohas C, Baudin E 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; 28: 69-76.

64. Kulke MH, Ruszniewski P, Van Cutsem E et al. A randomized, open-label, phase 2 study of everolimus in combination with pasireotide LAR or everolimus alone in advanced, well-differentiated, progressive pancreatic neuroendocrine tumors: COOPERATE-2 trial. Ann Oncol 2017; 28: 1309-1315.

65. Yao JC, Shah MH, Ito T et al. Everolimus for advanced pancreatic neuroendocrine tumors. N Engl J Med 2011; 364: 514-523.

66. Yao JC, Pavel M, Lombard-Bohas C et al. Everolimus for the Treatment of Advanced Pancreatic Neuroendocrine Tumors: Overall Survival and Circulating Biomarkers From the Randomized, Phase III RADIANT-3 Study. J Clin Oncol 2016; 34: 3906-3913.

67. Yao JC, Fazio N, Singh S et al. Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. Lancet 2016; 387: 968-977.

68. Singh S, Carnaghi C, Buzzoni R et al. Everolimus in neuroendocrine tumors of the gastrointestinal tract and unknown primary. Neuroendocrinology 2018; 106: 211-220.

69. Pavel ME, Singh S, Strosberg JR et al. Health-related quality of life for everolimus versus placebo in patients with advanced, non-functional, well-differentiated gastrointestinal or lung neuroendocrine tumours (RADIANT-4): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2017; 18: 1411-1422.

70. Meric-Bernstam F, Akcakanat A, Chen H et al. PIK3CA/PTEN mutations and Akt activation as markers of sensitivity to allosteric mTOR inhibitors. Clin Cancer Res 2012; 18: 1777-1789.

71. Pavel ME, Hainsworth JD, Baudin E 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; 378: 2005-2012.

72. Pavel ME, Baudin E, Oberg KE et al. Efficacy of everolimus plus octreotide LAR in patients with advanced neuroendocrine tumor and carcinoid syndrome: final overall survival from the randomized, placebo-controlled phase 3 RADIANT-2 study. Ann Oncol 2017; 28: 1569-1575.

73. EMA. https://www.ema.europa.eu/en/documents/product-information/afinitor-epar-product-information_en.pdf.

74. Panzuto F, Rinzivillo M, Spada F et al. Everolimus in Pancreatic Neuroendocrine Carcinomas G3. Pancreas 2017; 46: 302-305.

75. Raymond E, Dahan L, Raoul JL et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. N Engl J Med 2011; 364: 501-513.

76. Faivre S, Niccoli P, Castellano D et al. Sunitinib in pancreatic neuroendocrine tumors: updated progression-free survival and final overall survival from a phase III randomized study. Ann Oncol 2017; 28: 339-343.

77. Vinik A, Bottomley A, Korytowsky B et al. Patient-reported outcomes and quality of life with sunitinib versus placebo for pancreatic neuroendocrine tumors: results from an International Phase III Trial. Target Oncol 2016; 11: 815-824.

78. EMA. https://ec.europa.eu/health/documents/community-register/2016/20161109136193/anx_136193_en.pdf.

79. Raymond E, Kulke MH, Qin S et al. Efficacy and safety of sunitinib in patients with well-differentiated pancreatic neuroendocrine tumours. Neuroendocrinology 2018; 107: 237-245.

80. Pellat A, Dreyer C, Couffignal C et al. Clinical and Biomarker Evaluations of Sunitinib in Patients with Grade 3 Digestive Neuroendocrine Neoplasms. Neuroendocrinology 2018; 107: 24-31.

81. Xu J, Shen L, Zhou Z et al. Efficacy and safety of surufatinib in patients with well-differentiated advanced extrapancreatic neuroendocrine tumors (NETs): Results from the randomized phase III study (SANET-ep). Ann Oncol 2019; 30: v851-v934.

82. Lamarca A, Elliott E, Barriuso J et al. Chemotherapy for advanced non-pancreatic well-differentiated neuroendocrine tumours of the gastrointestinal tract, a systematic review and meta-analysis: A lost cause? Cancer Treat Rev 2016; 44: 26-41.

83. Moertel CG, Lefkopoulo M, Lipsitz S et al. Streptozocin-doxorubicin, streptozocin-fluorouracil or chlorozotocin in the treatment of advanced islet-cell carcinoma. N Engl J Med 1992; 326: 519-523.

84. Clewemar Antonodimitrakis P, Sundin A, Wassberg C et al. Streptozocin and 5-Fluorouracil for the Treatment of Pancreatic Neuroendocrine Tumors: Efficacy, Prognostic Factors and Toxicity. Neuroendocrinology 2016; 103: 345-353.

85. Dilz LM, Denecke T, Steffen IG et al. Streptozocin/5-fluorouracil chemotherapy is associated with durable response in patients with advanced pancreatic neuroendocrine tumours. Eur J Cancer 2015; 51: 1253-1262.

86. Cives M, Ghayouri M, Morse B et al. Analysis of potential response predictors to capecitabine/temozolomide in metastatic pancreatic neuroendocrine tumors. Endocr Relat Cancer 2016; 23: 759-767.

87. Kunz PL, Catalano PJ, Nimeiri HS et al. A randomized study of temozolomide or temozolomide and capecitabine in patients with advanced pancreatic neuroendocrine tumors: A trial of the ECOG-ACRIN Cancer Research Group (E2211). J Clin Oncol 2015; 33: TPS4145-TPS4145.

88. Walter T, van Brakel B, Vercherat C et al. O6-Methylguanine-DNA methyltransferase status in neuroendocrine tumours: prognostic relevance and association with response to alkylating agents. Br J Cancer 2015; 112: 523-531.

89. Sorbye H, Strosberg J, Baudin E et al. Gastroenteropancreatic high-grade neuroendocrine carcinoma. Cancer 2014; 120: 2814-2823.

90. Garcia-Carbonero R, Sorbye H, Baudin E et al. ENETS Consensus Guidelines for High-Grade Gastroenteropancreatic Neuroendocrine Tumors and Neuroendocrine Carcinomas. Neuroendocrinology 2016; 103: 186-194.

91. Knigge U, Capdevila J, Bartsch DK et al. ENETS Consensus recommendations for the standards of care in neuroendocrine neoplasms: follow-up and documentation. Neuroendocrinology 2017; 105: 310-319.

92. van Adrichem RC, Kamp K, van Deurzen CH et al. Is there an additional value of using somatostatin receptor subtype 2a immunohistochemistry compared to somatostatin receptor scintigraphy uptake in predicting gastroenteropancreatic neuroendocrine tumor response? Neuroendocrinology 2016; 103: 560-566.

93. Strosberg J, El-Haddad G, Wolin E et al. Phase 3 Trial of (177)Lu-Dotatate for midgut neuroendocrine tumors. N Engl J Med 2017; 376: 125-135.

94. EMA. https://www.ema.europa.eu/en/documents/overview/lutathera-epar-summary-public_en.pdf. Accessed November 29, 2019.

95. Hicks RJ, Kwekkeboom DJ, Krenning E et al. ENETS Consensus guidelines for the standards of care in neuroendocrine neoplasia: peptide receptor radionuclide therapy with radiolabeled somatostatin analogues. Neuroendocrinology 2017; 105: 295-309.

96. Kwekkeboom DJ, de Herder WW, Kam BL et al. Treatment with the radiolabeled somatostatin analog [177 Lu-DOTA 0,Tyr3]octreotate: toxicity, efficacy, and survival. J Clin Oncol 2008; 26: 2124-2130.

97. Brabander T, van der Zwan WA, Teunissen JJM et al. Long-Term Efficacy, Survival, and Safety of [(177)Lu-DOTA(0),Tyr(3)]octreotate in Patients with Gastroenteropancreatic and Bronchial Neuroendocrine Tumors. Clin Cancer Res 2017; 23: 4617-4624.

98. Severi S, Grassi I, Nicolini S et al. Peptide receptor radionuclide therapy in the management of gastrointestinal neuroendocrine tumors: efficacy profile, safety, and quality of life. Onco Targets Ther 2017; 10: 551-557.

99. Thang SP, Lung MS, Kong G et al. Peptide receptor radionuclide therapy (PRRT) in European Neuroendocrine Tumour Society (ENETS) grade 3 (G3) neuroendocrine neoplasia (NEN) - a single-institution retrospective analysis. Eur J Nucl Med Mol Imaging 2018; 45: 262-277.

100. Carlsen EA, Fazio N, Granberg D et al. Peptide receptor radionuclide therapy in gastroenteropancreatic NEN G3: a multicenter cohort study. Endocr Relat Cancer 2019; 26: 227-239.

101. Nicolini S, Severi S, Ianniello A et al. Investigation of receptor radionuclide therapy with (177)Lu-DOTATATE in patients with GEP-NEN and a high Ki-67 proliferation index. Eur J Nucl Med Mol Imaging 2018; 45: 923-930.

102. Zhang J, Kulkarni HR, Singh A et al. Peptide receptor radionuclide therapy in grade 3 neuroendocrine neoplasms: safety and survival analysis in 69 patients. J Nucl Med 2019; 60: 377-385.

103. Oberg K, Califano A. A Meta-analysis of the accuracy of a neuroendocrine tumor nRNA genomic biomarker (NETest) in blood. Ann Oncol 2019.

104. Bodei L, Kidd MS, Singh A et al. PRRT genomic signature in blood for prediction of (177)Lu-octreotate efficacy. Eur J Nucl Med Mol Imaging 2018; 45: 1155-1169.

105. Bodei L, Kidd MS, Singh A et al. PRRT neuroendocrine tumor response monitored using circulating transcript analysis: the NETest. Eur J Nucl Med Mol Imaging 2020; 47: 895-906.

106. van Treijen MJC, Korse CM, van Leeuwaarde RS et al. Blood transcript profiling for the detection of neuroendocrine tumors: results of a large independent validation study. Front Endocrinol (Lausanne) 2018; 9: 740.

Table 1. WHO 2019 classification for gastroenteropancreatic NENs [9]

Morphology	**Grade**	**Mitotic count (2 mm²)[a]**	**Ki-67 Index (%)[b]**
Well-differentiated NETs	G1	<2	<3
Well-differentiated NETs	G2	2–20	3–20
Well-differentiated NETs	G3	>20	>20
Poorly-differentiated NECs • Small-cell • Large-cell	G3	>20	>20
MiNEN			
Tumour-like lesions			

HPF, high-power field; MiNEN, mixed neuroendocrine/nonendocrine neoplasm; NEC, neuroendocrine carcinoma; NEN, neuroendocrine neoplasm; NET, neuroendocrine tumour; WHO, World Health Organization.

[a]10 HPF=2 mm^2, at least 40 fields (at x40 magnification) evaluated in areas of highest mitotic density.

[b]MIB1 antibody; percentage of 500–2000 tumour cells in areas of highest nuclear labelling.

Table 2. Biomarkers

Biomarker	Method	Use	LoE, GoR
Ki-67 (MIB1)	IHC	Prognostic relevance, essential component of the WHO grading for NENs	IV, A
SSTR-2/5	IHC	Detection of somatostatin receptors when no functional imaging is possible	IV, C
DAXX/ATRX	IHC	Prognostic relevance for Pan-NETs; distinction from NEC	IV, C
P53/pRb	IHC	Classification of poorly-differentiated NECs or distinction from NET G3	IV, C
MGMT	IHC, promoter methylation assay	Predictive value for temozolomide response	IV, D

GoR, grade of recommendation; IHC, immunohistochemistry; LoE, level of evidence; MGMT, O6-methylguanine-DNA methyltransferase; NEC, neuroendocrine carcinoma; NEN, neuroendocrine neoplasm; NET, neuroendocrine tumour; Pan-NET, pancreatic neuroendocrine tumour; P53, tumour protein; pRb, retinoblastoma protein; SSTR, somatostatin receptor; WHO, World Health Organization.

Adapted from Kloeppel et al. [8] with permission.

Table 3. Clinical classification of GEP-NETs by site of origin and by hormonal secretion

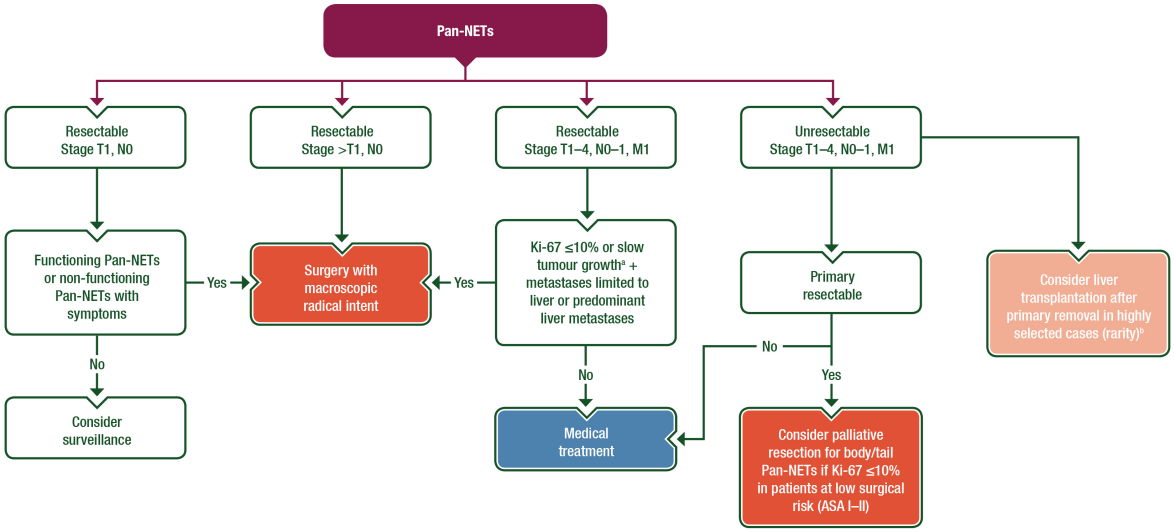
	Frequency	**Symptoms**	**Secretory product**
Intestinal NETs (carcinoids)	50% of GEP-NETs		
With CS	20%	Flushing, diarrhoea, endocardial fibrosis, wheezing	Prostaglandin, tachykinin, substance P, serotonin, histamine, kinins CgA[a]
Without CS	80%	Unspecific abdominal pain	CgA[a]
Pan-NETs	30% of GEP-NETs		
Functioning	10%–30%	Zollinger-Ellison syndrome	Gastrin
		Hypoglycaemia	Insulin
		Necrolytic erythema Hyperglycaemia	Glucagon
		WDHA syndrome	VIP
		Diabetes, gall stones, diarrhoea	Somatostatin
		Cushing syndrome	CRH, ACTH

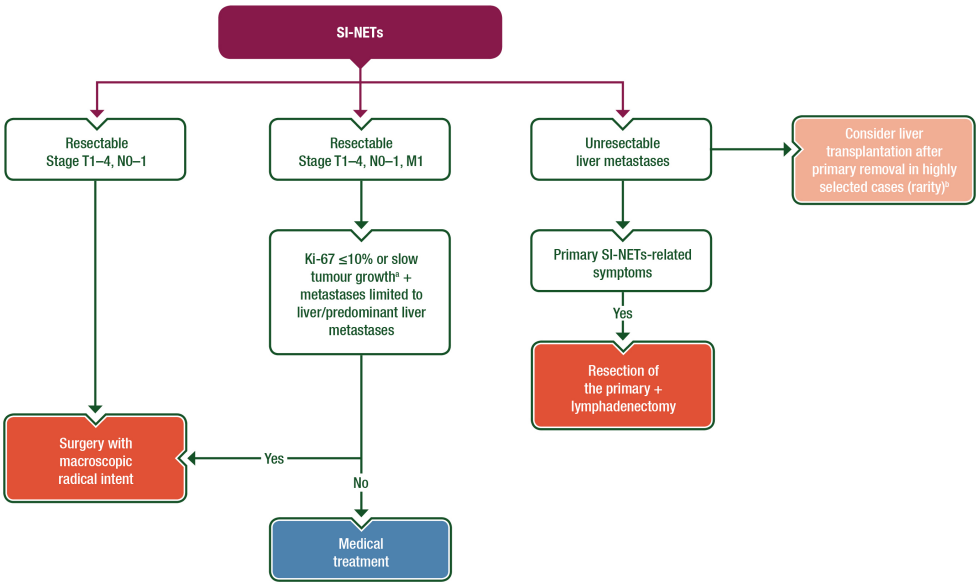
		Acromegaly	GHRH, GH
		Hypercalcaemia	PTHrP
		Flushing, diarrhoea	Calcitonin[b] Serotonin CgA[a]
NF	70%–90%	Unspecific abdominal pain Rarely jaundice, weight loss	CgA[a] PP[c]

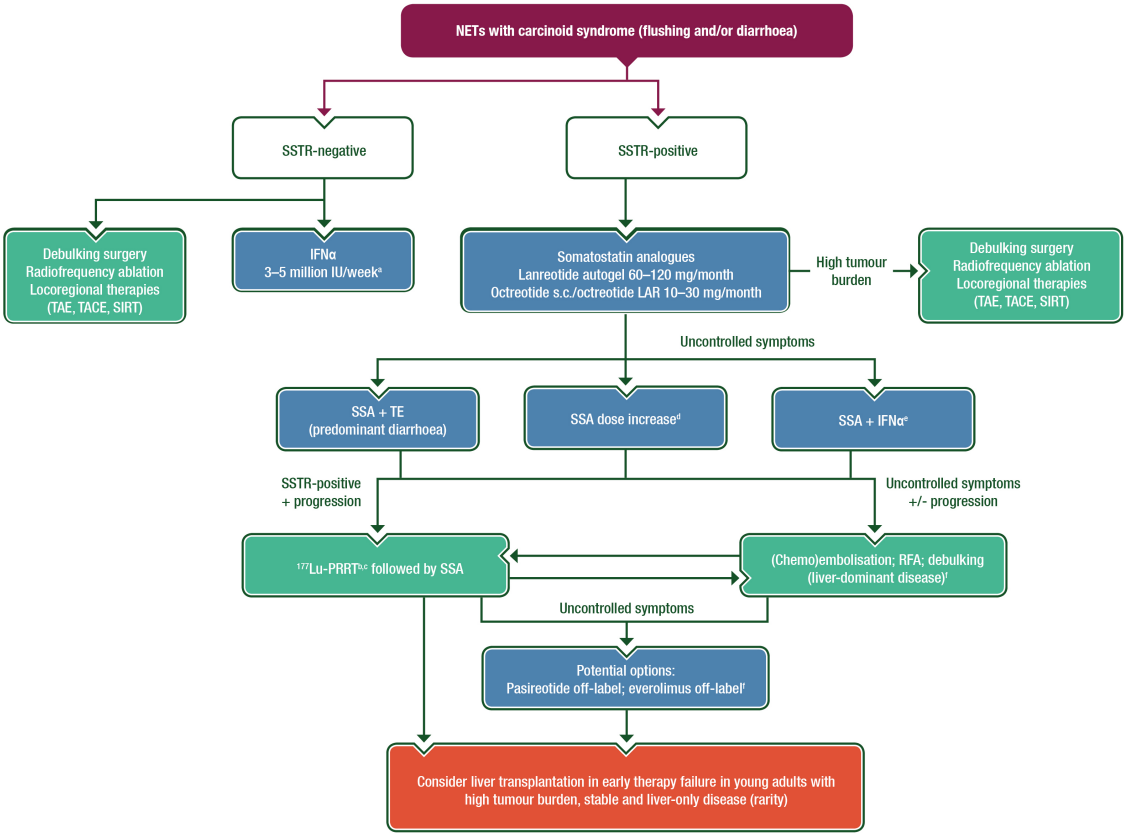
ACTH, adrenocorticotropic hormone; CgA, chromogranin A; CRH, corticotropin-releasing hormone; CS, carcinoid syndrome; GEP, gastroenteropancreatic; GEP-NET, gastroenteropancreatic neuroendocrine tumour; GH, growth hormone; GHRH, growth hormone-releasing hormone; GI-NET, gastrointestinal neuroendocrine tumour; NET, neuroendocrine tumour; NF, non-functioning; Pan-NET, pancreatic neuroendocrine tumour; PP, pancreatic polypeptide; PTHrP, parathyroid hormone-related peptide; VIP, vasoactive intestinal peptide; WDHA syndrome, watery diarrhoea, hypokalaemia, achlorhydria.

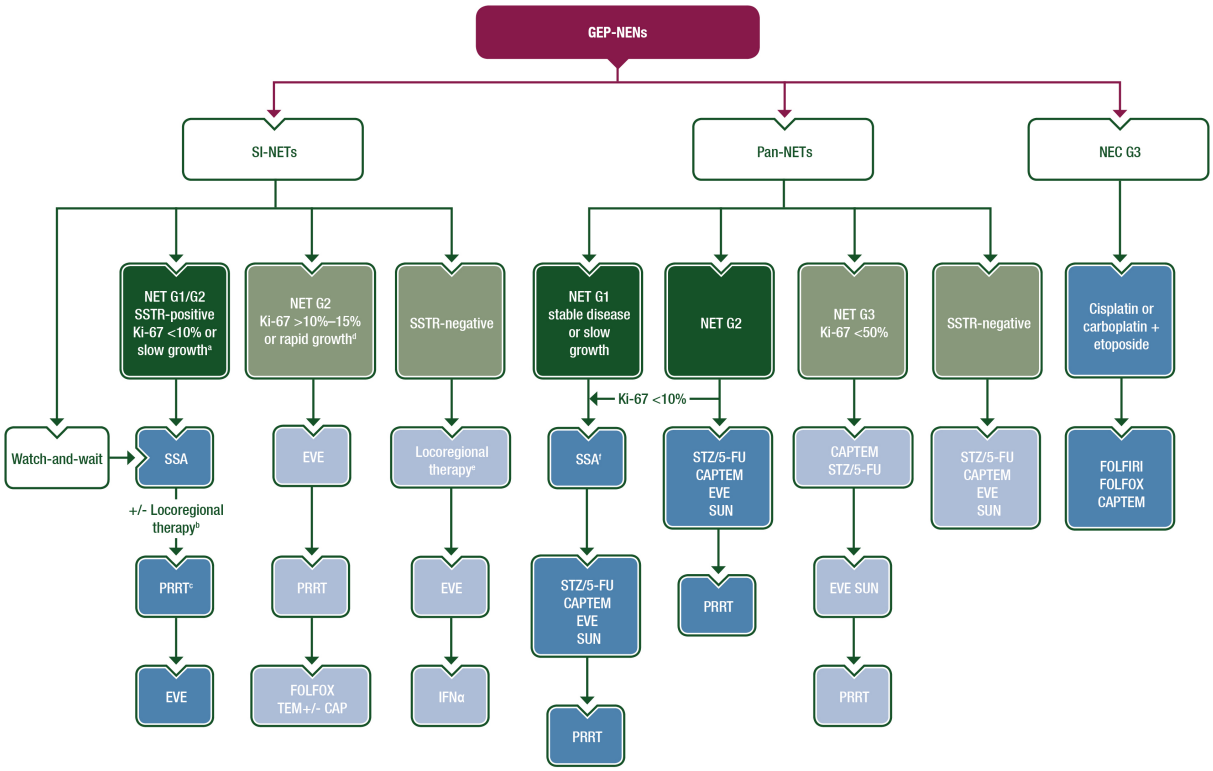
[a]CgA is secreted by functioning and NF tumours.

[b]Calcitonin-secreting tumours may present as NF tumours. [c]PP can also be elevated in GI-NETS.


Pan-NETs
Resectable Stage T1, N0
Resectable Stage >T1, N0
Resectable Stage T1–4, N0–1, M1
Unresectable Stage T1–4, N0–1, M1
Functioning Pan-NETs or non-functioning Pan-NETs with symptoms
Yes
Surgery with macroscopic radical intent
Yes
Ki-67 ≤10% or slow tumour growth[a] + metastases limited to liver or predominant liver metastases
Primary resectable
Consider liver transplantation after primary removal in highly selected cases (rarity)[b]
No
Consider surveillance
No
Medical treatment
No
Yes
Consider palliative resection for body/tail Pan-NETs if Ki-67 ≤10% in patients at low surgical risk (ASA I–II)


SI-NETs
Resectable
Stage T1–4, N0–1
Resectable
Stage T1–4, N0–1, M1
Unresectable
liver metastases
Consider liver transplantation after primary removal in highly selected cases (rarity)[b]
Ki-67 ≤10% or slow tumour growth[a] + metastases limited to liver/predominant liver metastases
Primary SI-NETs-related symptoms
Yes
Resection of the primary + lymphadenectomy
Surgery with macroscopic radical intent
Yes
No
Medical treatment


NETs with carcinoid syndrome (flushing and/or diarrhoea)
SSTR-negative
SSTR-positive
Debulking surgery
Radiofrequency ablation
Locoregional therapies
(TAE, TACE, SIRT)
IFNα
3–5 million IU/week[a]
Somatostatin analogues
Lanreotide autogel 60–120 mg/month
Octreotide s.c./octreotide LAR 10–30 mg/month
High tumour burden
Debulking surgery
Radiofrequency ablation
Locoregional therapies
(TAE, TACE, SIRT)
Uncontrolled symptoms
SSA + TE
(predominant diarrhoea)
SSA dose increase[d]
SSA + IFNα[e]
SSTR-positive
+ progression
Uncontrolled symptoms
+/- progression
177Lu-PRRT[b,c] followed by SSA
(Chemo)embolisation; RFA; debulking
(liver-dominant disease)[f]
Uncontrolled symptoms
Potential options:
Pasireotide off-label; everolimus off-label[f]
Consider liver transplantation in early therapy failure in young adults with
high tumour burden, stable and liver-only disease (rarity)


GEP-NENs
SI-NETs
Pan-NETs
NEC G3
NET G1/G2 SSTR-positive Ki-67 <10% or slow growth[a]
NET G2 Ki-67 >10%–15% or rapid growth[d]
SSTR-negative
NET G1 stable disease or slow growth
NET G2
NET G3 Ki-67 <50%
SSTR-negative
Cisplatin or carboplatin + etoposide
Ki-67 <10%
Watch-and-wait
SSA
+/- Locoregional therapy[b]
PRRT[c]
EVE
EVE
PRRT
FOLFOX TEM+/- CAP
Locoregional therapy[e]
EVE
IFNα
SSA[f]
STZ/5-FU CAPTEM EVE SUN
PRRT
STZ/5-FU CAPTEM EVE SUN
PRRT
CAPTEM STZ/5-FU
EVE SUN
PRRT
STZ/5-FU CAPTEM EVE SUN
FOLFIRI FOLFOX CAPTEM