

SPECIAL ARTICLE

## Gastroenteropancreatic neuroendocrine neoplasms: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up<sup>†</sup>

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### 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 NENs (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.<sup>1</sup> The incidence of localised and regional NENs has increased more than that of NENs with distant metastasis.<sup>1</sup> The incidence of gastroenteropancreatic NETs (GEP-NETs) in the USA 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.<sup>1</sup> 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.<sup>2–4</sup>

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 NETs (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%.<sup>5</sup> Recently, whole genomic sequencing revealed 17% of apparently sporadic Pan-NETs carried germline mutations also including DNA repair genes (e.g. *MUTYH*, *CHEK2*, *BRCA2*).<sup>6</sup>

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**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 of age) 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 hematoxylin 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.<sup>7</sup> 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.<sup>8,9</sup> 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).<sup>8</sup> The separation of well-differentiated NET G3 from NEC, which had been valid exclusively for Pan-NENs, has now been adopted for

**Table 1. WHO 2019 classification for gastroenteropancreatic NENs<sup>9</sup>**

Morphology	Grade	Mitotic count (2 mm <sup>2</sup> ) <sup>a</sup>	Ki-67 Index (%) <sup>b</sup>
Well-differentiated NETs	G1	<2	<3
Well-differentiated NETs	G2	2–20	3–20
Well-differentiated NETs	G3	>20	>20
Poorly-differentiated NECs	G3	>20	>20

• Small-cell  
• Large-cell

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.

<sup>a</sup> 10 HPF = 2 mm<sup>2</sup>, at least 40 fields (at ×40 magnification) evaluated in areas of highest mitotic density.

<sup>b</sup> 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 Kloepffel<sup>8</sup> with permission.

gastrointestinal (GI) NENs in an update of the WHO classification for GI NENs.<sup>9</sup> 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<sup>2</sup> 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.<sup>8</sup> 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).<sup>8</sup> 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.<sup>10</sup>

**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

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

	Frequency	Symptoms	Secretory product
<b>Intestinal NETs (carcinoids)</b>	50% of GEP-NETs		
With CS	20%	Flushing Diarrhoea Endocardial fibrosis Wheezing	Prostaglandin, tachykinin, substance P Serotonin Serotonin Histamine, kinins CgA <sup>a</sup>
Without CS	80%	Unspecific abdominal pain	CgA <sup>a</sup>
<b>Pan-NETs</b>	30% of GEP-NETs		
Functioning	10%–30%	Zollinger-Ellison syndrome Hypoglycaemia Necrolytic erythema Hyperglycaemia WDHA syndrome Diabetes, gallstones, diarrhoea Cushing syndrome Acromegaly Hypercalcaemia Flushing Diarrhoea	Gastrin Insulin Glucagon VIP Somatostatin CRH, ACTH GHRH, GH PTHrP Calcitonin <sup>b</sup> Serotonin CgA <sup>a</sup>
NF	70%–90%	Unspecific abdominal pain Rarely jaundice, weight loss	CgA <sup>a</sup> PP <sup>c</sup>

ACTH, adrenocorticotropic hormone; CgA, chromogranin A; CRH, corticotropin-releasing hormone; CS, carcinoid syndrome; 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.

<sup>a</sup> CgA is secreted by functioning and NF tumours.

<sup>b</sup> Calcitonin-secreting tumours may present as NF tumours.

<sup>c</sup> PP can also be elevated in GI-NETs.

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<sup>11</sup> for various types of GEP-NETs. For all NECs, the staging system of adenocarcinomas must be applied.<sup>11</sup> 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 NETs (SI-NETs) (see supplementary Tables S1–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.<sup>12</sup> 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.<sup>13</sup> The sensitivity of CT to detect NETs is 61%–93% and the specificity is 71%–100%.<sup>12,14,15</sup> The detection rate for liver metastases (LMs) is 79% (73%–

94%),<sup>16,17</sup> and for extra-abdominal soft tissue metastases, the sensitivity is 70% (60%–100%) and specificity 96% (range 87%–100%).<sup>18</sup> 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%),<sup>19–21</sup> 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%).<sup>22–26</sup> 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.<sup>12</sup> 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 carried out. 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<sup>27</sup> 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.

Imaging by <sup>68</sup>Ga/<sup>64</sup>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].<sup>12</sup> 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 <sup>68</sup>Ga-DOTA-SSA-PET-CT is 92% (range 64%–100%) and specificity 95% (range 83%–100%).<sup>28</sup> The sensitivity to detect pancreatic and duodenal NETs is 92% and the specificity 83%,<sup>28</sup> and the corresponding values for bone metastases are 97%–100% and 92%–100%.<sup>28</sup> The use of PET with [<sup>18</sup>F]fluoro-deoxyglucose (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.<sup>29</sup> 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.<sup>29–31</sup>

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 <sup>68</sup>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].
  - <sup>68</sup>Ga/<sup>64</sup>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 liver, pancreas, brain and bone lesions, 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**

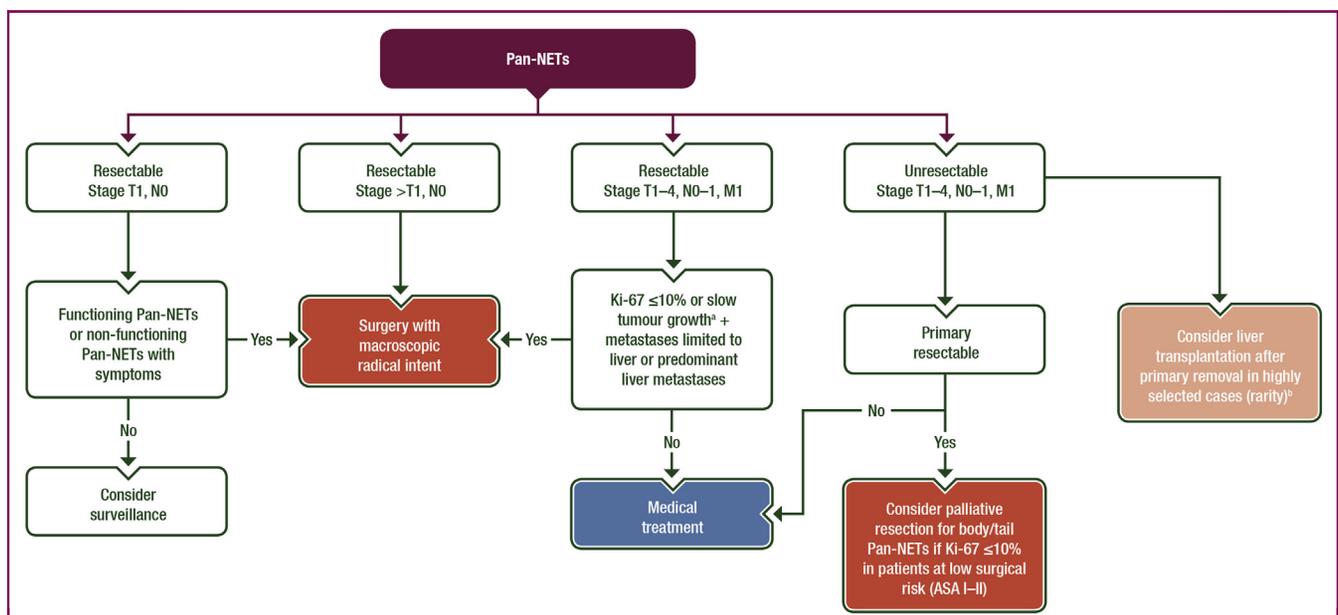
Surgery is the treatment of choice for local or locoregional disease in NET G1 and G2. In functional NETs, clinical symptoms should be managed before any intervention [IV, A].

**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.<sup>32,33</sup> 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].<sup>33</sup> 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.<sup>34</sup> A standard pancreatectomy (pancreatico-duodenectomy or distal pancreatectomy) with



**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.

<sup>a</sup> 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.

<sup>b</sup> 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.

regional lymphadenectomy<sup>35</sup> is recommended for Pan-NETs >2 cm [IV, A]. Enucleation may represent an alternative approach to standard pancreatectomy in selected cases.<sup>36</sup> 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.<sup>37</sup>

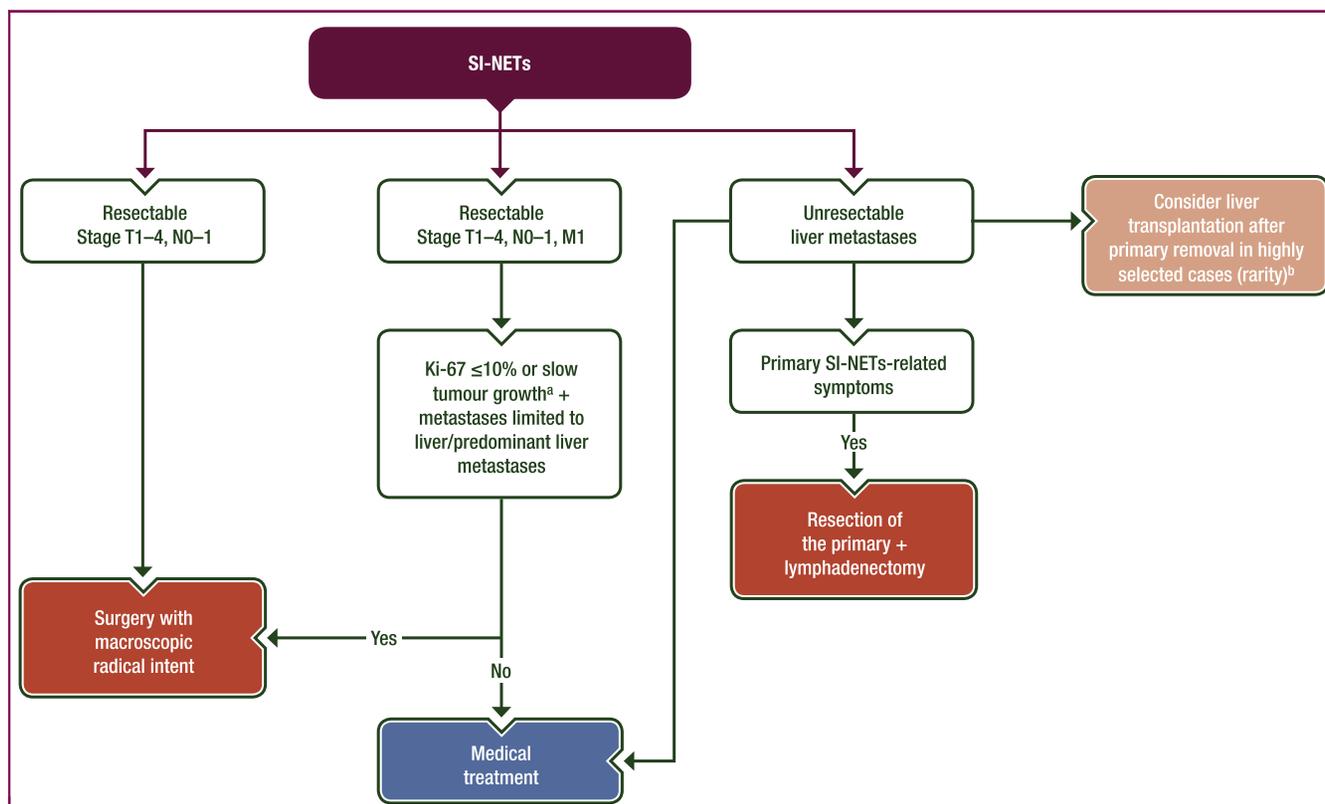
For Pan-NETs in patients affected by MEN1 syndrome, see Section 1 of [supplementary Material](#), available at *Annals of Oncology* online.

## SI-NETs

Macroscopic radical resection of localised SI-NETs reduces the risk of intestinal complications (bowel obstruction and ischaemia), is associated with improved outcomes<sup>38</sup> 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.<sup>39</sup> During surgery for SI-NETs, an accurate palpation of the entire intestine and a systematic lymphadenectomy (at least 8 nodes) are mandatory.<sup>39,40</sup> 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-NETs and regional lymph nodes can be achieved in ≤80% of cases if carried out by experienced surgeons.<sup>40</sup>

## Recommendations

- Surgery is the treatment of choice for local or locoregional disease in NET G1 and G2. Before any



**Figure 2. Surgical approach in SI-NETs.**

NET, neuroendocrine tumour; RECIST, response evaluation criteria in solid tumours; SI-NET, small intestinal neuroendocrine tumour.

<sup>a</sup> 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.

<sup>b</sup> 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.

intervention, medical treatment is required in functionally active tumours [IV, A].

- For NF-Pan-NETs  $\leq 2$  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  $\leq 2$  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-NETs, surgery also plays a role in metastatic disease.<sup>41</sup> 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].<sup>42</sup> 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.<sup>43</sup> Surgical resection should be attempted in the presence of resectable or potentially resectable LMs.<sup>43</sup> A curative resection (R0, R1) of GEP-NETs with LMs is associated with a 5-year overall survival (OS) rate of around 85%.<sup>41</sup> 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.<sup>44</sup>

The role of debulking surgery in advanced NF-GEP-NETs is unclear.<sup>38,41</sup> 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.<sup>45</sup>

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 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 before transplant consideration and age  $< 60$  years [IV, B].<sup>20</sup> In these selected patients with good baseline prognostic factors, a 5-year OS of 69%–97.2% has been reported.<sup>46</sup> Liver transplantation 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). Liver transplantation 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 chemotherapy (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.<sup>47</sup> 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<sup>48</sup> 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.<sup>49</sup> Furthermore, interferon alpha (IFN- $\alpha$ ) 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].<sup>50</sup>

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 ( $\geq 4$  bowel movements per day) compared with placebo. Durable response (defined as  $\geq 30\%$  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 (t.i.d.), respectively.<sup>51</sup> 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.<sup>52</sup> Patients with durable response

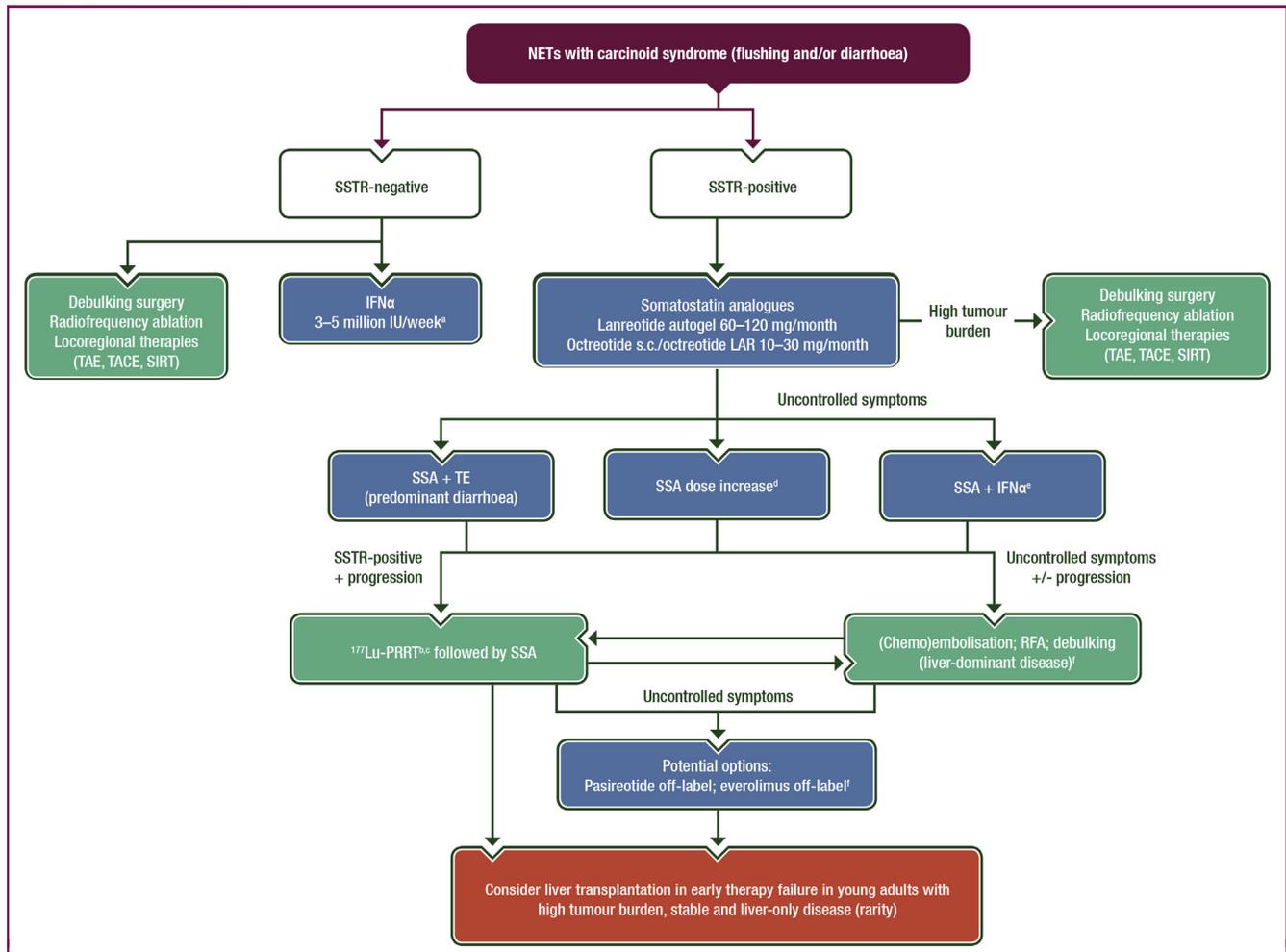
showed significant and/or meaningful improvements in global quality of life (QoL), as well as nausea, pain, diarrhoea and other GI symptoms.<sup>53</sup> Telotristat ethyl (250 mg t.i.d.) is approved for treatment of diarrhoea associated with CS in patients insufficiently controlled with SSA and can 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).<sup>54,55</sup> 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 (<sup>177</sup>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.<sup>55</sup> 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, IFN- $\alpha$ , 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.<sup>56</sup> 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 Pan-NETs refractory to SSA.<sup>57</sup>

**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 SSTR 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- $\alpha$  (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



**Figure 3. Therapeutic approach in NETs with carcinoid syndrome.**

<sup>177</sup>Lu, lutetium-177; IFN- $\alpha$ , 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.

<sup>a</sup> 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).

<sup>b</sup> Long-acting SSAs should be interrupted at least 4 weeks before PRRT and should be continued 'not earlier than' 1 h after PRRT cycle(s).

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

<sup>d</sup> 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.

<sup>e</sup> IFN- $\alpha$  should be interrupted if PRRT is considered.

<sup>f</sup> TE can be continued with other treatments if patient has a benefit; it is not an option if patient has predominant flushing.

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 anti-proliferative 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-naïve 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.<sup>58</sup>

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  $\leq$ 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.<sup>59</sup> The CLARINET extension study also showed efficacy in progressive disease patients with entero-pancreatic NETs.<sup>60</sup> There is very good long-term tolerability of both SSAs.<sup>47,58,59</sup> 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,<sup>59,61</sup> 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.

**IFN- $\alpha$ .** Based on long-term experience in NETs<sup>50</sup> and supported by recent results from a large randomised trial (including 35% midgut NET, median PFS 15.4 months for IFN- $\alpha$  and octreotide LAR),<sup>62</sup> IFN- $\alpha$  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/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 from 9.7 months in heavily pretreated patients (RADIANT-1 study) to 16.6 months in patients with few prior therapies.<sup>63,64</sup>

The registration trial (RADIANT-3 study) with 410 patients (including 40% therapy-naïve patients) showed prolongation of PFS by 6.4 months in advanced progressive Pan-NETs; median PFS was 11 months with everolimus and 4.6 months with placebo.<sup>65</sup> There was a trend toward OS benefit.<sup>66</sup> 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)<sup>64</sup>; 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 (STZ)-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.<sup>67</sup> 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. Everolimus should

be used in 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.<sup>68</sup> 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.<sup>69,70</sup>

The use of everolimus is less clear in patients with advanced NETs (carcinoids) associated with 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<sup>71</sup>; 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.<sup>72</sup>

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.<sup>73</sup> Across all randomised everolimus trials, drug-related adverse events were mostly manageable. However, around 60% required dose reduction or treatment interruption.<sup>65,67,71</sup> 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.<sup>74</sup> 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 significantly longer PFS (11.4 versus 5.5 months) was noticed in favour of sunitinib [I, A].<sup>75</sup> ORR was <10%; there was a trend toward an OS benefit with sunitinib.<sup>76</sup> 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.<sup>77</sup> 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.<sup>78</sup> Results of a phase IV trial confirm the efficacy and safety of sunitinib in patients with advanced, well-differentiated Pan-NETs who were treatment-naïve or previously treated with other drugs.<sup>79</sup> 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<sup>80</sup> 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).<sup>81</sup>

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%)<sup>82</sup>; 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 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.<sup>83–85</sup> From retrospective trials, temozolomide (TEM)-based ChT is active in Pan-NETs, either alone or combined with capecitabine (CAP)<sup>86</sup>; preliminary results from the prospective explorative two-arm phase II trial of CAPTEM versus TEM 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].<sup>87</sup> 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

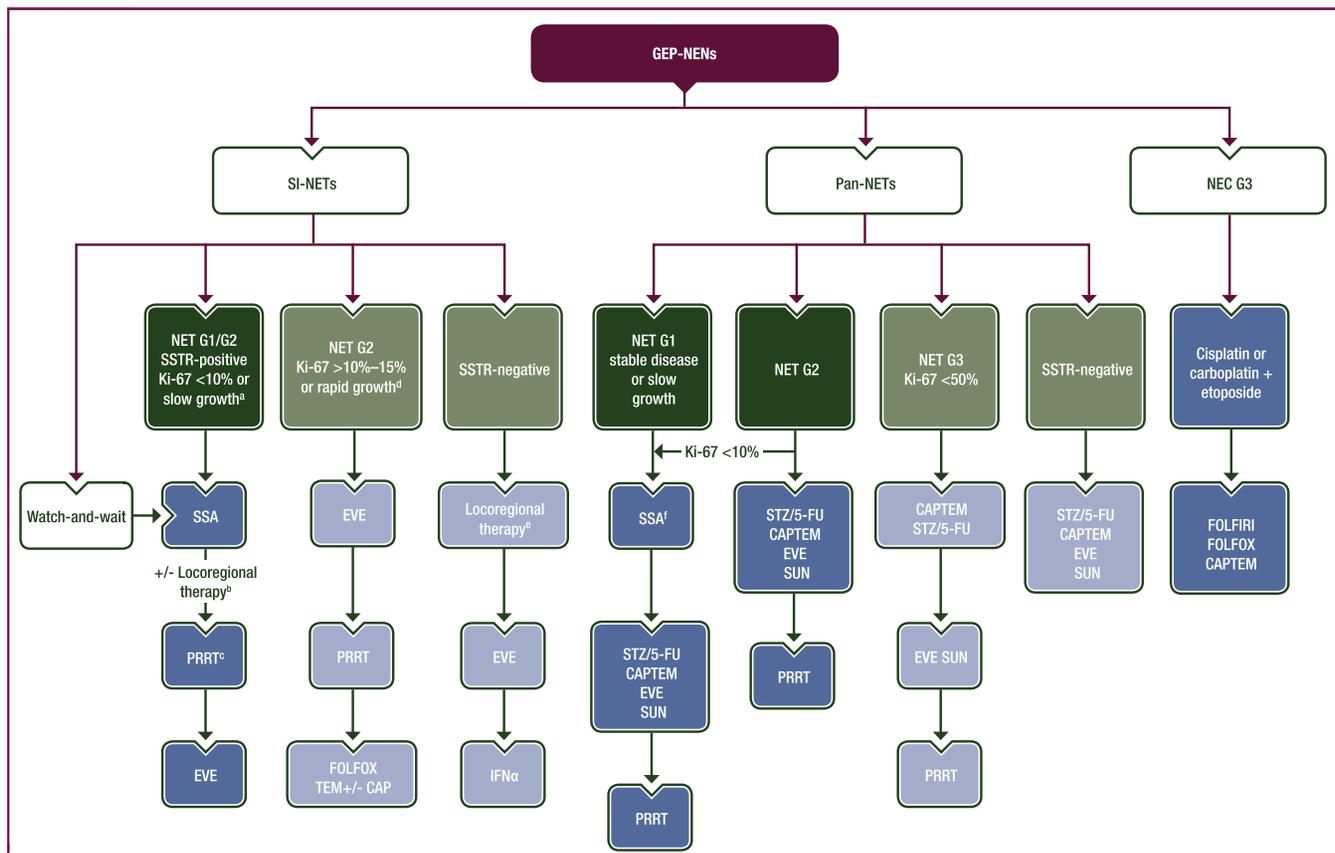
or promoter methylation for preselection of patients is controversial.<sup>86,88</sup>

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].<sup>89,90</sup>

The ORR with cisplatin-based ChT in NET G3 (in general, Ki-67 is <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.<sup>91,92</sup> The two peptides most commonly used for PRRT are DOTATOC and DOTATATE. <sup>177</sup>Lu is increasingly preferred to yttrium-90 (<sup>90</sup>Y)-labelled SSA due to 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 <sup>177</sup>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.<sup>93</sup> 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. <sup>177</sup>Lu-DOTATATE was superior to high-dose octreotide in terms of PFS (primary end point). Median PFS (mPFS) with <sup>177</sup>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).<sup>94</sup> <sup>177</sup>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.<sup>93,94</sup> Treatment was also associated with an improvement in symptoms and time to QoL deterioration for global health status, physical functioning, fatigue, pain and diarrhoea.<sup>55</sup> 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].<sup>95</sup> 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.<sup>54,96–98</sup> <sup>177</sup>Lu-DOTATATE has been approved by



**Figure 4. Systemic therapy in GEP-NENs.**

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<sup>2</sup>.

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

Green arrows indicate progressive disease.

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-NEN, gastroenteropancreatic neuroendocrine neoplasm; IFN- $\alpha$ , 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.

<sup>a</sup> Slow tumour growth is defined as stable disease by RECIST criteria for >1 year.

<sup>b</sup> In liver-dominant disease.

<sup>c</sup> If PRRT is not available, everolimus can be used as second-line therapy.

<sup>d</sup> Rapid growth is defined as RECIST progression within a year or less.

<sup>e</sup> In liver-only disease or predominant liver disease.

<sup>f</sup> If SSTR-positive.

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 SSTR-positive 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 four 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.<sup>99–102</sup> The overall results show disease control rates between 30% and 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,<sup>101</sup> and in patient subgroups with Ki-67 >55%, mPFS was 6 months, 4 months and 4 months, respectively from the different studies.<sup>99,100,102</sup> 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).

Treatment with <sup>177</sup>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].
- Liver transplantation 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 IFN- $\alpha$ , 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 before and 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 SSTR 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.
- IFN- $\alpha$  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 [I, A; ESMO-MCBS v1.1 score: 3]. In GI NETs, everolimus should be used in patients with clearly progressive disease [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-FU/leucovorin/irinotecan (FOLFIRI), 5-FU/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].
- <sup>177</sup>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 upfront for potentially resectable LMs or systemic therapy, or locoregional therapies. 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.<sup>103</sup>

### 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].

Imaging with <sup>68</sup>Ga/<sup>64</sup>Cu-SSTR-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.<sup>91,92</sup> 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 response to PRRT and detect residual disease after surgery and was superior to CgA in a validation study.<sup>104–106</sup>

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 3–6 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.<sup>107</sup> Levels of evidence and grades of recommendation have been applied using the system shown in [supplementary Table S5](#), available at *Annals of Oncology* online.<sup>108</sup> 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.

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