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THE HEART OF MEDICAL EDUCATION

TOOLS FOR OPTIMISING TREATMENT & MANAGEMENT OF ADVANCED NETS

MICRO LEARNING

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DEVELOPED BY NET CONNECT

This programme is developed by NET CONNECT, an international group of experts in the field of neuroendocrine tumours.

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THIS PROGRAMME HAS BEEN DEVELOPED BY THE FOLLOWING EXPERTS

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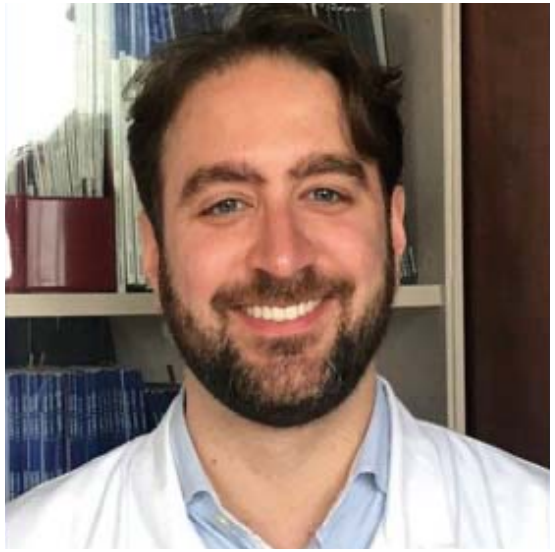


EDUCATIONAL OBJECTIVES

- Understand how to optimally manage advanced NETs
- Raise awareness of the criteria essential for assessing therapeutic success
- Highlight the tools available for clinicians to evaluate tumour evolution over time

NET, neuroendocrine tumour

CLINICAL TAKEAWAYS

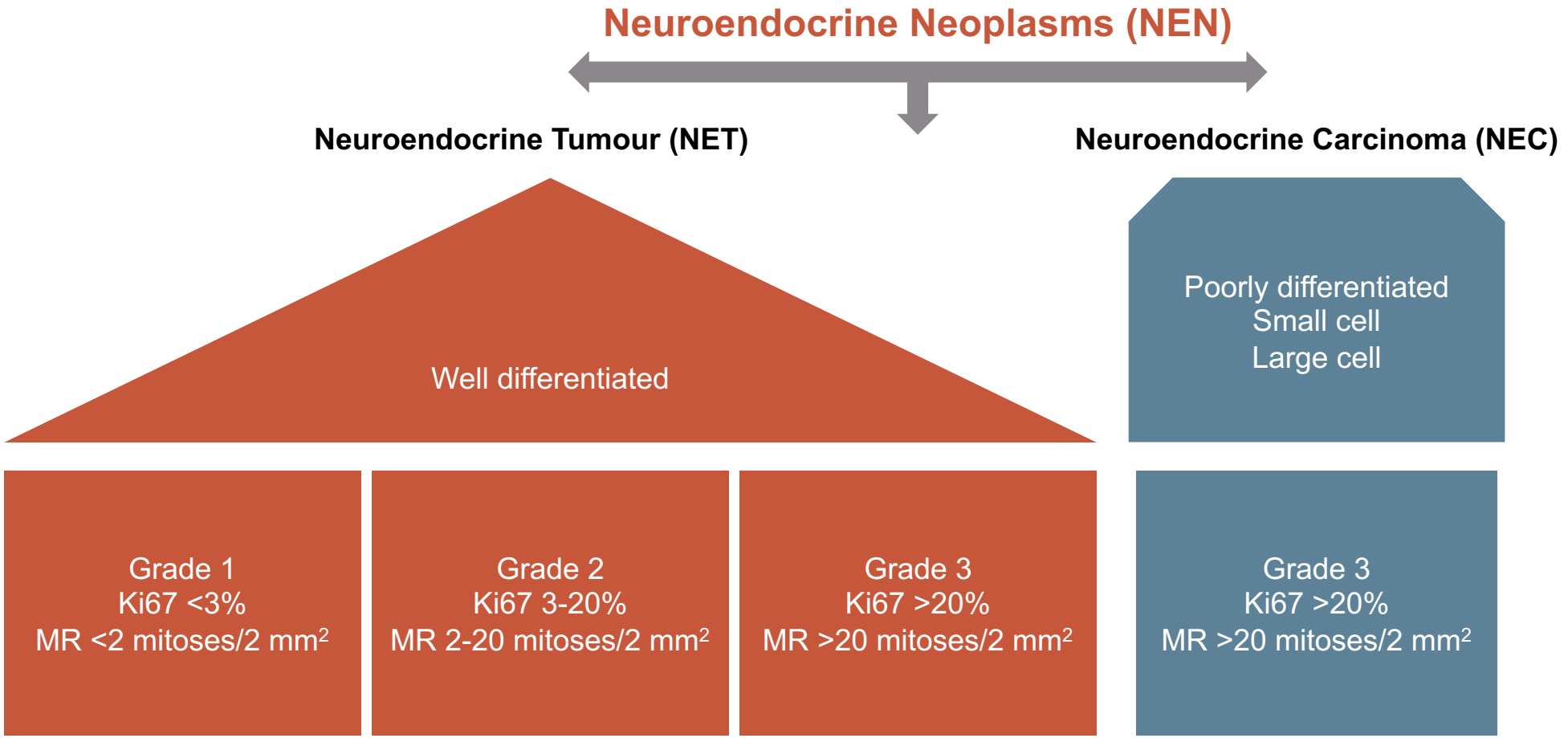
- Outcomes depend on tumour location, size, distribution, and hepatic extent of metastases as well as tumour growth rate
- Involvement of the patient, as well as a multidisciplinary team, in decision-making is essential
- Always take quality of life (QoL) and long-term toxicity into account when choosing therapy

NET, neuroendocrine tumour; QoL, quality of life

INTRODUCTION

Brief overview

CLASSIFICATION OF NENs (WHO 2022)



Mixed neuroendocrine-non-neuroendocrine neoplasms (MiNENs) were recognised for the first time in the 5th edition of the *WHO Classification of Endocrine and Neuroendocrine Tumors* to define mixed neoplasms arising in all systems of the body; descriptive and conceptual category rather than a specific diagnosis

Ki67, antigen Kiel 67; MR, mitotic rate; WHO, World Health Organization

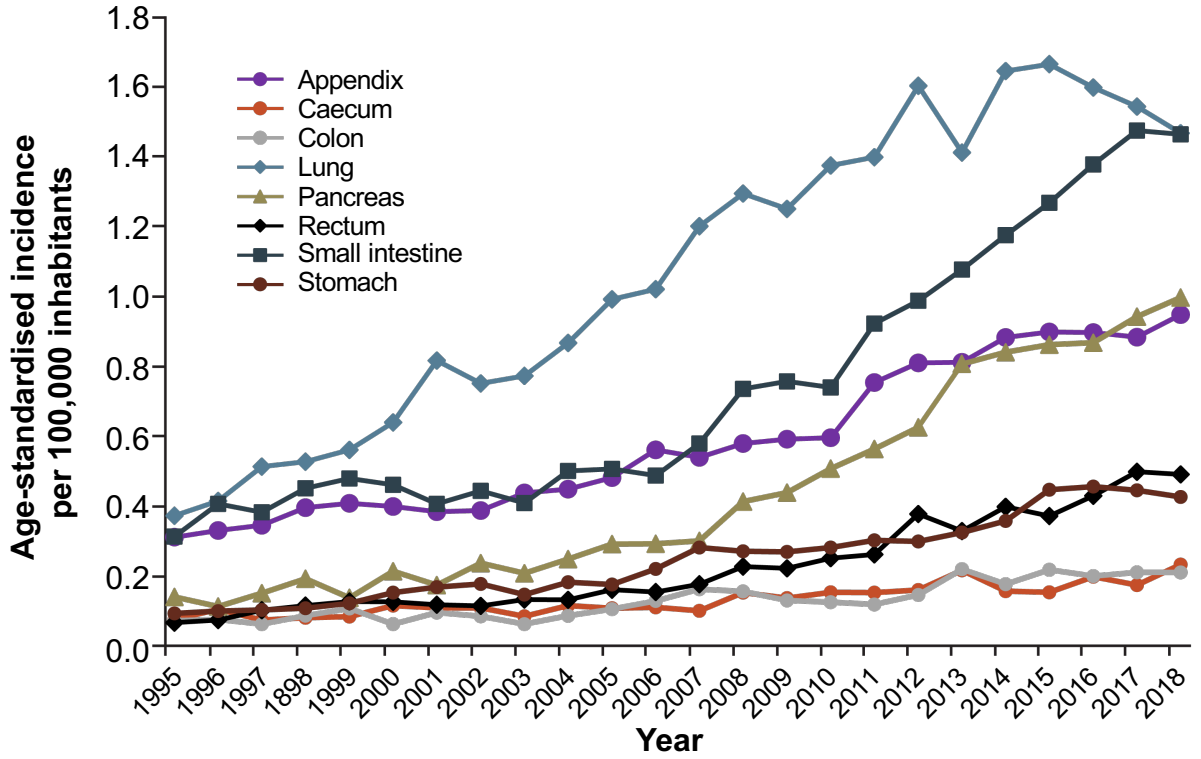
Rindi G, et al. Endocr Pathol. 2022;33:115-54; image adapted from Chauhan A, et al. CA Cancer J Clin. 2024 Apr 29, Epub ahead of print

EPIDEMIOLOGY: RARE TUMOURS

- Increasing incidence in recent years
  - Eight-fold increase in NETs over the past five decades[1]
  - Due (at least in part) to improvements in diagnosis and awareness[1]
  - Age-adjusted incidence increased 3.7-fold between 1995 and 2018, from 2.35 to 8.61 per 100,000[2]
- In the SEER 18 registry (2000-2012), gastroenteropancreatic neuroendocrine tumours (GEP-NETs) were the most common well differentiated NETs (3.56 per 100,000)[1]

NEN incidence rise over time

Age-standardised incidence by primary site of NEN in England 1995-2018[2]



Site	Appendix	Caecum	Colon	Lung	Pancreas	Rectum	Small Int	Stomach
Average change per year	105.2%	107.3%	107.6%	106.6%	110.6%	109.9%	107.5%	107.4%
Absolute increase	304%	305%	287%	393%	705%	725%	466%	453%

NEN, neuroendocrine neoplasm; NET, neuroendocrine tumour; SEER, Surveillance, Epidemiology, and End Results programme

1. Dasari A, et al. JAMA Oncol. 2017;3:1335-42; 2. White BE, et al. Lancet Reg Health Eur. 2022;23:100510

SIGNS AND SYMPTOMS

- When NETs cause clinical symptoms from secreted hormones, they are termed “functioning” tumours
- Most NETs do not produce a biologically active hormone and are termed “non-functioning”
- Some NETs cause non-specific symptoms (e.g. abdominal pain, fatigue)
- Most NETs do not cause symptoms and are thus diagnosed incidentally

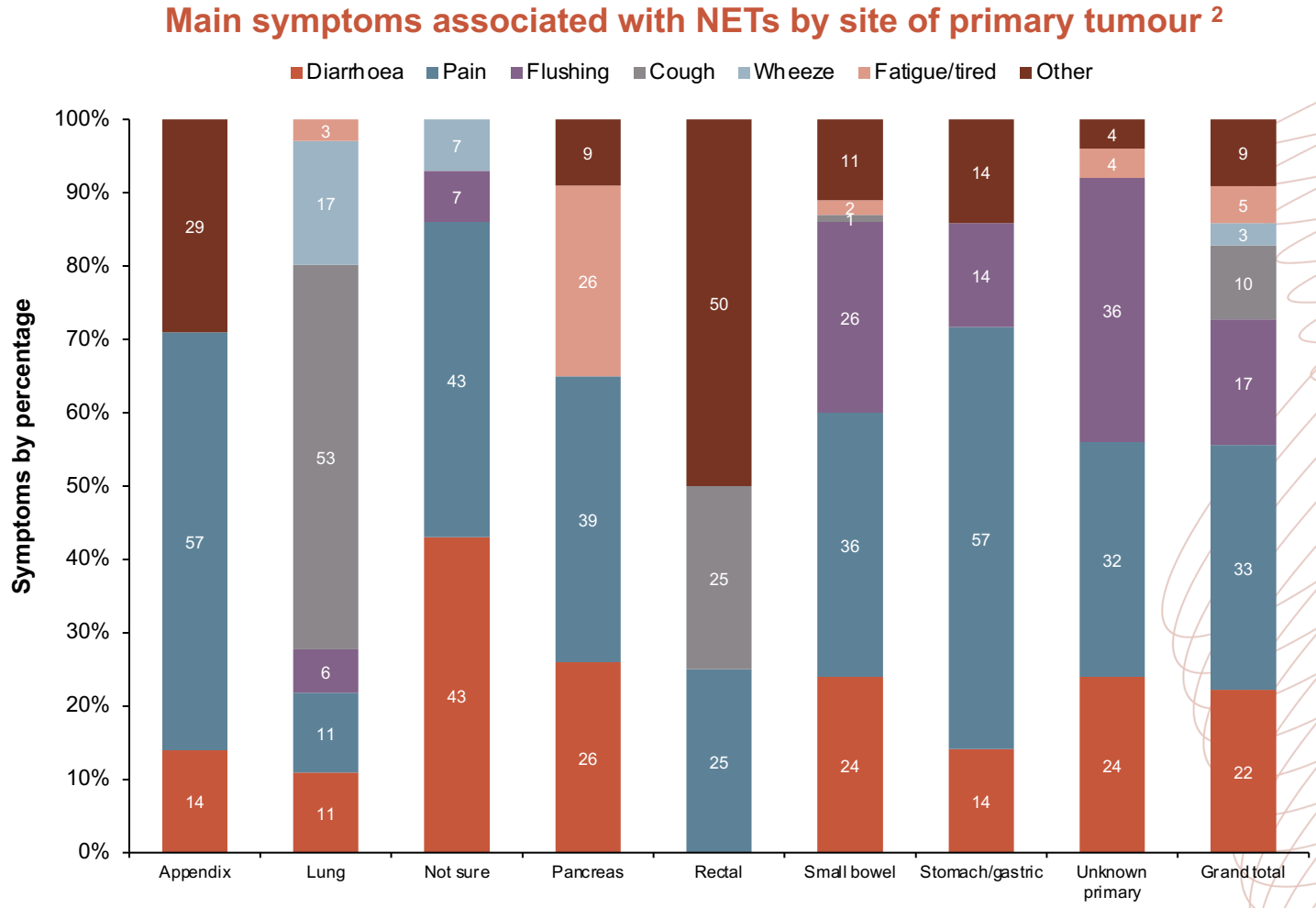


Image adapted from: Basuroy R, et al. BMC Cancer. 2018;18:1122

SIGNS AND SYMPTOMS: SOME NETS ARE FUNCTIONAL

Functional NET syndromes

Tumour location	Hormone	Symptoms and signs	Syndrome
Foregut	5-HTP, histamine	Pruritus, cutaneous wheals, bronchospasm	Carcinoid syndrome
Small intestine, lung	Serotonin, tachykinin, prostaglandins	Flushing, diarrhoea, valvular disease, bronchospasm	Carcinoid syndrome
Pancreatic β cells	Insulin, proinsulin	Hypoglycaemic symptoms	Insulinoma, Whipple triad
Gastrinoma triangle	Gastrin	Diarrhoea, peptic ulcer disease	Gastrinoma, Zollinger–Ellison
Pancreatic α cells	Glucagon	Diabetes, deep vein thrombosis, depression, dermatitis (necrolytic migratory erythema)	Glucagonoma, 4D syndrome
Pancreatic δ cells	Somatostatin	Diabetes, cholelithiasis, steatorrhea, weight loss, achlorhydria	Somatostatinoma
Non-β islet cells	Vasoactive intestinal peptide	Watery diarrhoea (profuse), hypokalaemia, achlorhydria	VIPoma Verner–Morrison (WDHA syndrome)
Lung	ACTH	Fat redistribution/obesity, facial plethora, skin atrophy/easy bruising/striae, proximal myopathy hyperglycaemia	Cushing syndrome

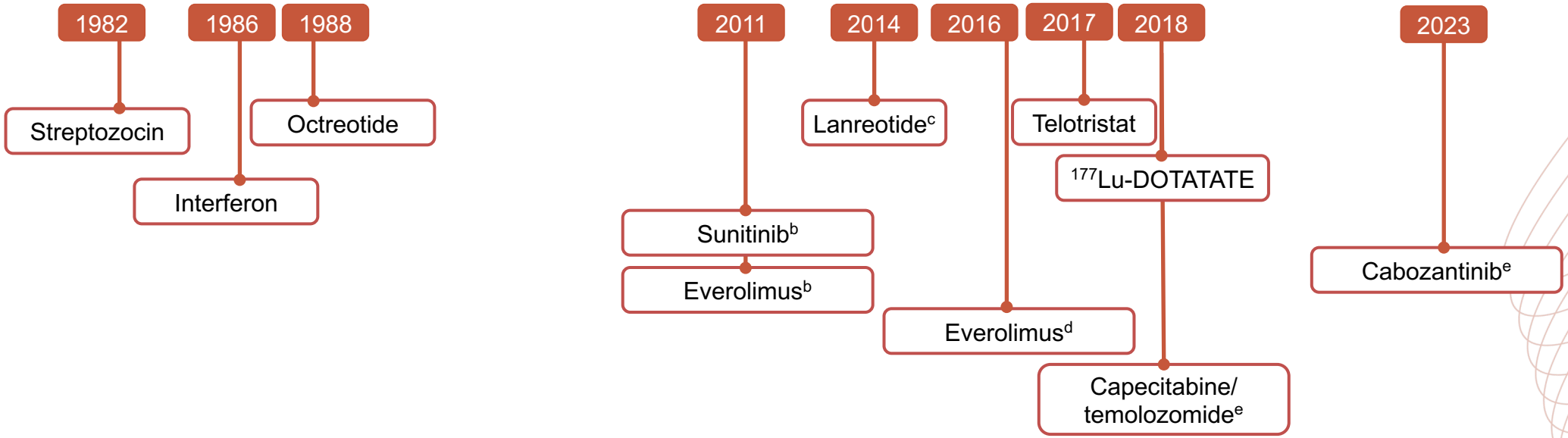
4D syndrome, glucagonoma syndrome; 5-HTP, 5-hydroxytryptophan; ACTH(oma), adrenocorticotropic hormone(-producing pancreatic neuroendocrine neoplasm); NET, neuroendocrine tumour; VIPoma, vasoactive intestinal peptide-secreting tumour; WDHA, watery diarrhoea, hypokalaemia, achlorhydria

Raphael MJ, et al. CMAJ. 2017;189:E398-E404

SURVIVAL HAS IMPROVED AS THE NET TREATMENT LANDSCAPE HAS EVOLVED

- Patients[a] diagnosed between 2009-2012 had better OS compared with those diagnosed between 2000-2004, with a 21.3% lower risk of death (HR=0.79; 95% CI, 0.73-0.85)[c]

Key milestones in NET therapeutics



[a] In the United States; [b] For (p)NETs; [c] For GEP-NETs; d gastrointestinal and thoracic NETs; [e] Not yet EMA/FDA-approved or used routinely in clinical practice but has been shown in a phase III study to improve progression-free survival for patients living with NETs

177Lu, lutetium-177; CI, confidence interval; EMA, European Medicines Agency; GEP, gastroenteropancreatic neuroendocrine, HR, hazard ratio; (p)NET, (pancreatic) neuroendocrine tumour

1. Dasari A, et al. JAMA Oncol. 2017;3:1335-42; 2. Adapted from: Chauhan A, et al. Cancers (Basel). 2022;14:5248

NOTES TO ASSIST THERAPEUTIC DECISION-MAKING

- Lanreotide is FDA- and EMA-approved for Grade 1 and Grade 2 (Ki67 ≥10%) GEP-NETs of midgut, pancreatic or unknown origin, in adult patients with unresectable locally advanced or metastatic disease[1]
- Octreotide is EMA-approved for progressive unresectable or metastatic, well-differentiated (Grade 1 or Grade 2) non-functional NETs of gastrointestinal or lung origin in adults (FDA-approved only for hormone control)[2]
- ^{177}Lu-DOTATATE is FDA- and EMA-approved for adults with unresectable or metastatic, progressive, well-differentiated (Grade 1 and Grade 2), somatostatin receptor positive-GEP-NETs[1]
  - Efficacy of PRRT may be limited in the setting of bulky liver disease[3]
- Everolimus is FDA- and EMA-approved for progressive unresectable or metastatic, well-differentiated (Grade 1 or Grade 2) non-functional NETs of gastrointestinal or lung origin[1]
- Sunitinib is FDA- and EMA-approved for adults with unresectable or metastatic, well differentiated pancreatic neuroendocrine tumours with disease progression[1]
- Chemotherapy is predominantly used to treat pancreatic NETs
  - Streptozocin-based therapy can be used, but nephrotoxicity can be limiting, and it is not routinely available in the USA
  - Alternative alkylating agent-based chemotherapy combinations (capecitabine–temozolomide, dacarbazine–5-FU) are now routinely administered with similar efficacy and better tolerance

^{177}Lu, lutetium-177; 5-FU, 5-fluorouracil; EMA, European Medical Agency; FDA, Food and Drug Administration; GEP-NET, gastroenteropancreatic neuroendocrine tumour; Ki67, antigen Kiel 67; NET, neuroendocrine tumour; PRRT, peptide receptor radionuclide therapy

1. https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-for-solid-tumours/esmo-mcbs-scorecards/ (accessed April 2024); 2. Zhang, JY, Kunz PL. JCO Oncol Pract. 2022;18:258-64; 3. Strosberg J, et al. N Engl J Med. 2017;376:125-35

THERAPEUTIC DECISION-MAKING

SEVERAL ORGANIZATIONS HAVE PUBLISHED GUIDELINES REGARDING THERAPY FOR NETS

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

- Four *Clinical Practice Guidelines* on neuroendocrine tumours that include information on incidence, diagnosis, staging and risk assessment, treatment, response evaluation, and follow-up[1]
  - Adrenocortical carcinomas and malignant pheochromocytomas
  - Gastroenteropancreatic neuroendocrine neoplasms
  - Lung and thymic carcinoids
  - Thyroid cancer

NCCN National Comprehensive Cancer Network®

- NCCN Guidelines for *Neuroendocrine and Adrenal Gland Tumors* focus on diagnosis, treatment, and management of NETs, adrenal tumours, pheochromocytomas, paragangliomas, and multiple endocrine neoplasia[2]

ESMO, European Society for Medical Oncology; NET, neuroendocrine tumour

1. https://www.esmo.org/guidelines/guidelines-by-topic/endocrine-and-neuroendocrine-cancers (accessed April 2024); 2. Shah MH, et al. J Natl Compr Canc Netw. 2021;19:839-68

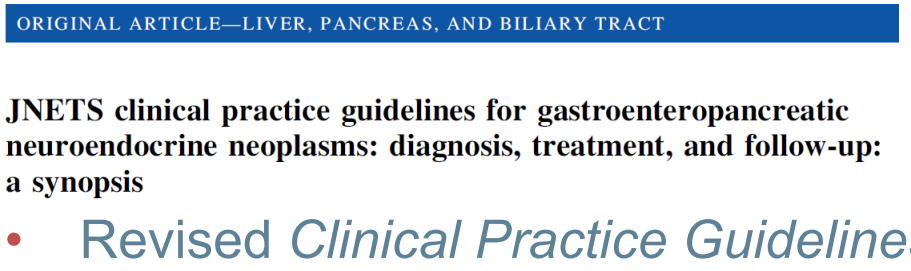
SEVERAL ORGANIZATIONS HAVE PUBLISHED GUIDELINES REGARDING THERAPY FOR NETS

ENETS EUROPEAN NEUROENDOCRINE TUMOR SOCIETY

- Seven new ENETS guidance papers on the management of NETs published in 2022-2023[1]

NANETS NORTH AMERICAN NEUROENDOCRINE TUMOR SOCIETY

- Thirteen guidelines and white paper summaries published by NANETS since 2010[2]


ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

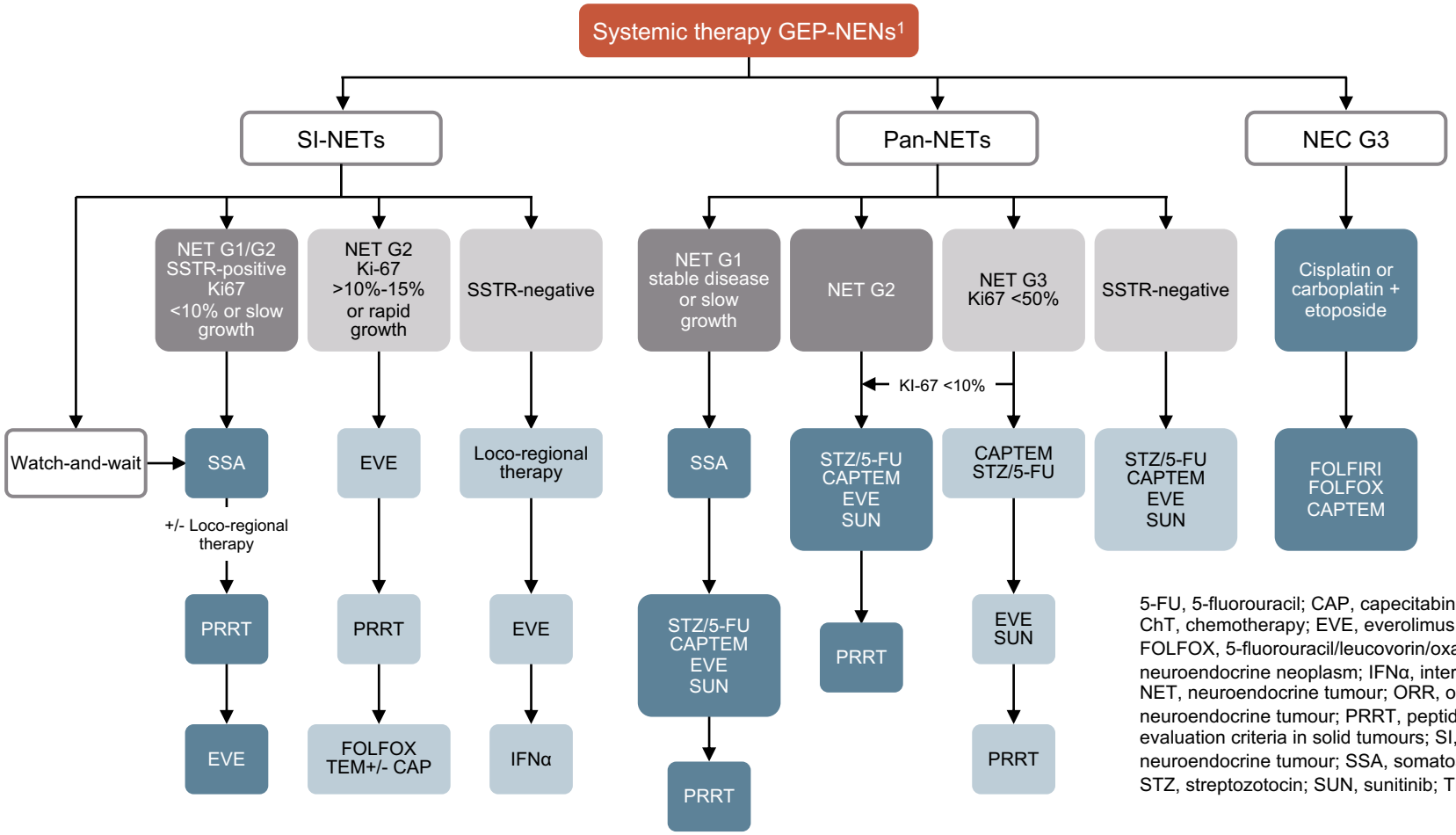
JNETS clinical practice guidelines for gastroenteropancreatic neuroendocrine neoplasms: diagnosis, treatment, and follow-up: a synopsis

- Revised *Clinical Practice Guidelines for Gastroenteropancreatic Neuroendocrine Neoplasms (GEP-NENs)* from the JNETS comprise chapters on diagnosis, pathology, surgical treatment, medical and multidisciplinary treatment, and MEN1/VHL disease[3]

JNETS, Japanese Neuroendocrine Tumor Society; MEN1, multiple endocrine neoplasia type 1; NET, neuroendocrine tumour; VHL, von Hippel-Lindau syndrome

1. https://www.enets.org/guidelines.html (accessed April 2024); 2. https://nanets.net/net-guidelines-library (accessed April 2024); 3. Ito T, et al. J Gastroenterol. 2021;56:1033-44

SAMPLE GUIDELINE FOR TREATMENT OF GEP-NENs: ESMO GUIDELINES (2020)



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; 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.

Evidence for treatment sequencing is limited[2]

NET heterogeneity means that such algorithms are useful for general guidance, but treatments should be considered on a case-by-case basis

ESMO, European Society for Medical Oncology

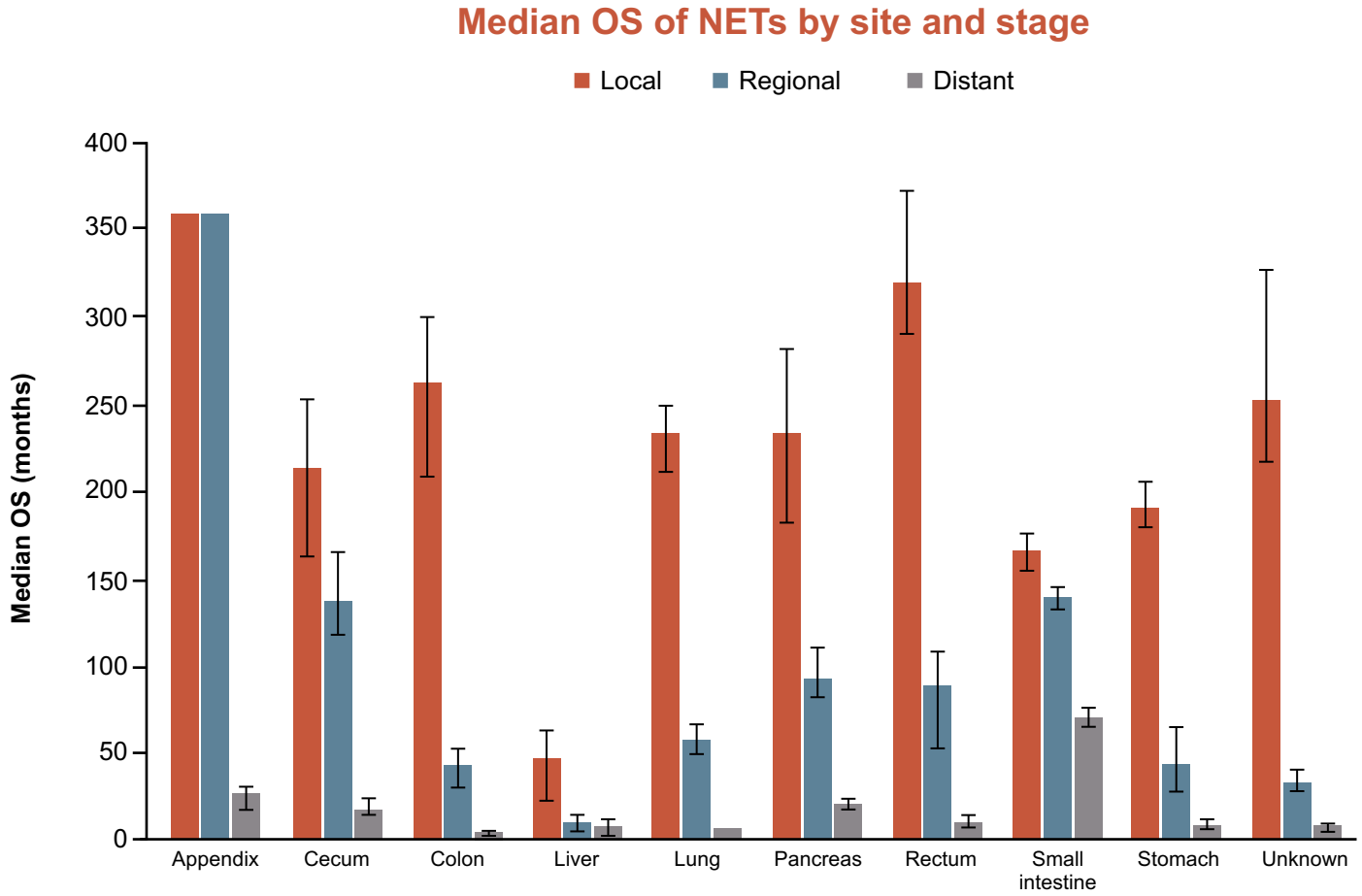
1. Pavel et al. Ann Oncol. 2020;31:844-60; 2. Riechelmann RP, et al. Am Soc Clin Oncol Educ Book. 2023;43:e389278

FACTORS TO CONSIDER IN THE CONTEXT OF THERAPEUTIC DECISION-MAKING

TUMOUR-RELATED FACTORS

TUMOUR-RELATED FACTORS: PRIMARY SITE AND STAGE

OVERALL SURVIVAL VARIES ACCORDING TO PRIMARY TUMOUR LOCATION AND STAGE



CI, confidence interval; GEP-NET, gastroenteropancreatic neuroendocrine tumour; HR, hazard ratio; NET, neuroendocrine tumour; OS, overall survival

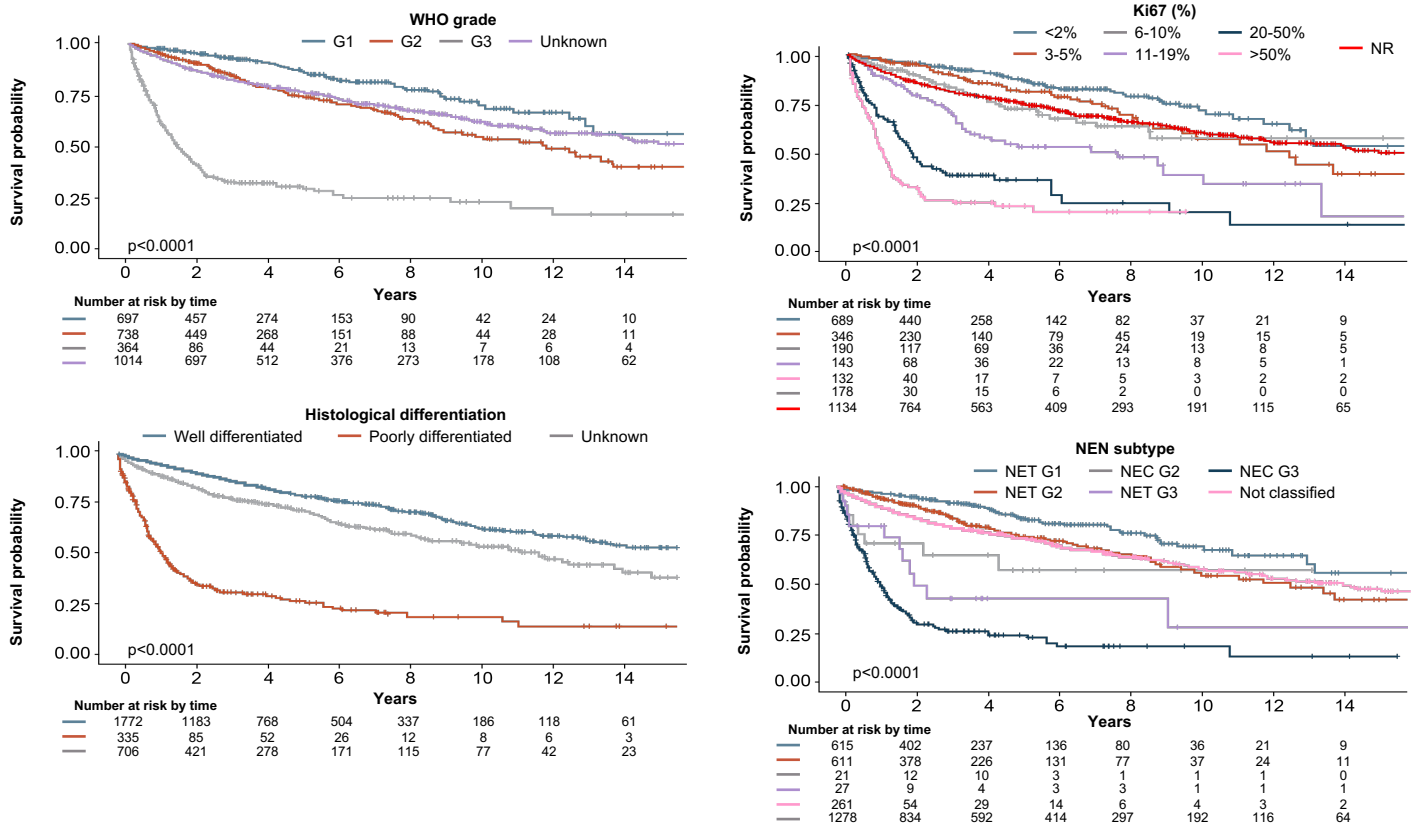
Dasari A, et al. JAMA Oncol. 2017;3:1335-42

TUMOUR-RELATED FACTORS: GRADE, DIFFERENTIATION, PROLIFERATION INDEX

HISTOLOGICAL DIFFERENTIATION AND KI67 PROLIFERATION INDEX HAVE PROGNOSTIC VALUE IN GEP-NENS

- Five-year survival has been shown to be significantly greater for NET-G2 versus poorly differentiated carcinomas (75.5% vs 58.2%) and NET-G3 versus NEC-G3 (43.7% vs 25.4%)[1]
- An increase in Ki67 index and high-grade progression may be important correlates of prognosis[2]

Overall survival by tumour differentiation and proliferation (GEP-NENs)[1]



Ki67, antigen Kiel 67; (GEP-)NEN, gastroenteropancreatic neuroendocrine neoplasm; NEC, neuroendocrine carcinoma; NET, neuroendocrine tumour; NR, not reported; WHO World Health Organisation

1. Nuñez-Valdovinos B, et al. Oncologist. 2018; 23:422-432; 2. Botling J, et al. Neuroendocrinology. 2020;110:891-98

TUMOUR-RELATED FACTORS: EXTENT AND LOCATION OF METASTASES AND TUMOUR GROWTH RATE

- Haematogenous spread to the liver parenchyma from a primary GEP-NET via the portal vein is common[1-3]
  - Liver-only disease in ~50% of patients[4]
  - Compared to other sites, patients with NET liver metastases have worse overall survival (HR=1.85; 95% CI, 1.46-2.36)[5,a]
- Size, distribution, and extent of liver metastases impact prognosis and therapeutic approach[1,4]
  - Palliative resection can be considered in selected patients
  - Liver-directed therapy reserved for those with adequate liver function, no portal vein thrombosis, and <70% liver involvement
    - Bland embolization, chemoembolization, and selective internal radiation therapy
- Location and extent of metastases matter in NETs
  - Consider liver-directed therapy for liver-dominant disease
  - Systemic pattern (e.g., bone, lung, lymph node, peritoneum) of disease warrants systemic therapy
  - Evaluate burden of disease: Low vs bulky disease
- Rate of growth
  - Assess tumour kinetics: Fast growing over weeks to months vs slow growing over years
  - Tumour Growth Rate (TGR) may be predictive for tumour progression and prognostic for survival in patients with NETs who are undergoing SSA treatment[6]

[a] Multivariable analysis with HRs calculated for 5-year mortality hazard rates, reference is lung (other sites: appendix, caecum, colon, pancreas, rectum, small intestine, stomach)

CI, confidence interval; GEP-NET, gastroenteropancreatic neuroendocrine tumour; HR, hazard ratio; NET, neuroendocrine tumour

1. Lewis MA and Hobday TJ. Int J Hepatol. 2012;2012:973946; 2. Mayo SC, et al. Ann Surg Oncol. 2010;17:3129-36; 3. John BJ and Davidson BR. Expert Rev Gastroenterol Hepatol. 2012;6:357-69; 4. Cazzato RL, et al. Cancers (Basel). 2021;13:6368; 5. Dasari A, et al. JAMA Oncol. 2017;3:1335-42; 6. Lamarca A, et al. Oncologist. 2019;24:e1082-e90

TUMOUR-RELATED FACTORS: PET IMAGING CHARACTERISTICS

- DOTA PET imaging for well differentiated NETs
  - Assesses somatostatin receptor (SSTR) expression and extent of disease
  - SSTR types 1 and 2 are highly expressed in >90% of GEP-NETs[1,2]
  - Imaging using SSTR PET (DOTA-) radiotracers is the gold standard in well-differentiated NETs
  - 68Ga/64Cu-DOTATATE and 68Ga-DOTATOC are approved SSTR PET tracers[3]
  - Routinely used to select patients for peptide receptor radionuclide therapy (PRRT)[4]

- [18F]FDG PET imaging for well differentiated NETs
  - Assesses glucose uptake, usually correlated to biological aggressiveness and Ki67 index
  - Can be useful as baseline scan:
    - In G3 NET to assess concordance with DOTA-PET uptake
    - In people living with NETs with low or no uptake on DOTA-PET or those with very unfavourable tumour biology
    - For G3 NET with very high Ki67 index (e.g. >55%), particularly if curative surgery is considered (and in some cases for response assessment)
  - In summary, FDG-PET should be performed in NETs if awareness of more biologically aggressive disease could influence the therapeutic decision[5]

[18F]FDG, fludeoxyglucose, fluorine-18; 64Cu, copper-64; 68Ga, gallium-68; G3, grade 3; GEP-NET, gastroenteropancreatic neuroendocrine tumour; Ki67, antigen Kiel 67; NEC, neuroendocrine carcinoma; NET, neuroendocrine tumour; PET, positron emission tomography; PRRT, peptide receptor radionuclide therapy; SSTR, somatostatin receptor

1. Reubi JC, et al. Eur J Nucl Med. 2001;28:836-46; 2. Zaknun JJ, et al. Eur J Nucl Med Mol Imaging. 2013;40:800-16; 3. Ambrosini V, et al. J Neuroendocrinol. 2024;36:e13359; 4. Hope TA, et al. J Nucl Med. 2023;64:204-10; 5. Rinzivillo M, et al. Oncologist. 2018;23:186-92

EXAMPLES OF OTHER POTENTIAL BIOMARKERS

- MGMT protein expression or *MGMT* promoter gene methylation (emerging biomarker)
  - ~50% of pNETs are MGMT-deficient[1]
  - MGMT enzyme deficiency may be associated with response in patients treated with alkylating agents (especially those living with pNETs)[1,2]
- Neuroendocrine neoplasms test (NETest)[4-8]
  - Multianalyte liquid biopsy that measures NET gene expression in blood
  - Under study as a biomarker of response to therapy and recurrent/residual disease following surgery
- PRRT Predictive Quotient (PPQ)[9,10]
  - PPQ integrates NET transcript expression in blood with tumour grade
  - Emerging data suggest baseline PPQ stratifies PRRT “responders” from “non-responders”

MAPK, mitogen-activated protein kinase; MGMT, methylguanine methyltransferase; NEN, neuroendocrine neoplasm; OS, overall survival; PFS, progression-free survival; (p)NET, (pancreatic) neuroendocrine tumour; PRRT, peptide receptor radionuclide therapy; SSA, somatostatin analogue

1. de Mestier L, et al. Endocr Relat Cancer. 2020;27:R391-405; 2. Kunz PL, et al. J Clin Oncol. 2023;41:1359-69; 3. Modlin IM, et al. Ann Surg Oncol. 2010;17:2427-4; 4. Bevere M, et al. Diagnostics (Basel). 2023;13:2820; 4. Modlin IM, et al. Endocrinol Metab Clin North Am. 2018;47:485-504; 5. Puliani G, et al. Neuroendocrinology. 2022;112:523-36; 6. Partelli S, et al. Ann Surg Oncol. 2020;27:3928-36; 7. Malczewska A, et al. Endocr Connect. 2019;8:442-53; 8. Malczewska A, et al. Endocr Connect. 2021;10:110-12; 9. Bodei L, et al. Eur J Nucl Med Mol Imaging. 2018;45:1155-69; 10. Bodei L. et al. J Nucl Med. 2023;64:567-73

PATIENT-RELATED FACTORS

PATIENT-RELATED FACTORS: HISTORY

- Predisposition: Some NETs arise in setting of hereditary cancer syndrome, for example:
  - GEP-NETs occur in 70-80% of patients with multiple endocrine neoplasia type 1 (MEN1) syndrome[1]
  - pNETs occur in 10-17% of patients with von Hippel-Lindau (VHL) disease[2]
  - The presence of a hereditary cancer syndrome can impact surgical decision-making
- Comorbidities
  - Liver or renal function impairment can impact choice of therapy[3]
    - e.g. careful with PRRT or capecitabine in the setting of renal dysfunction
  - Carcinoid heart disease is present in approximately 30-40% of patients with carcinoid syndrome[4]
  - Use caution when using with everolimus in the setting of poorly controlled diabetes
  - Avoid sunitinib in the setting of poorly controlled hypertension, angina, or stroke

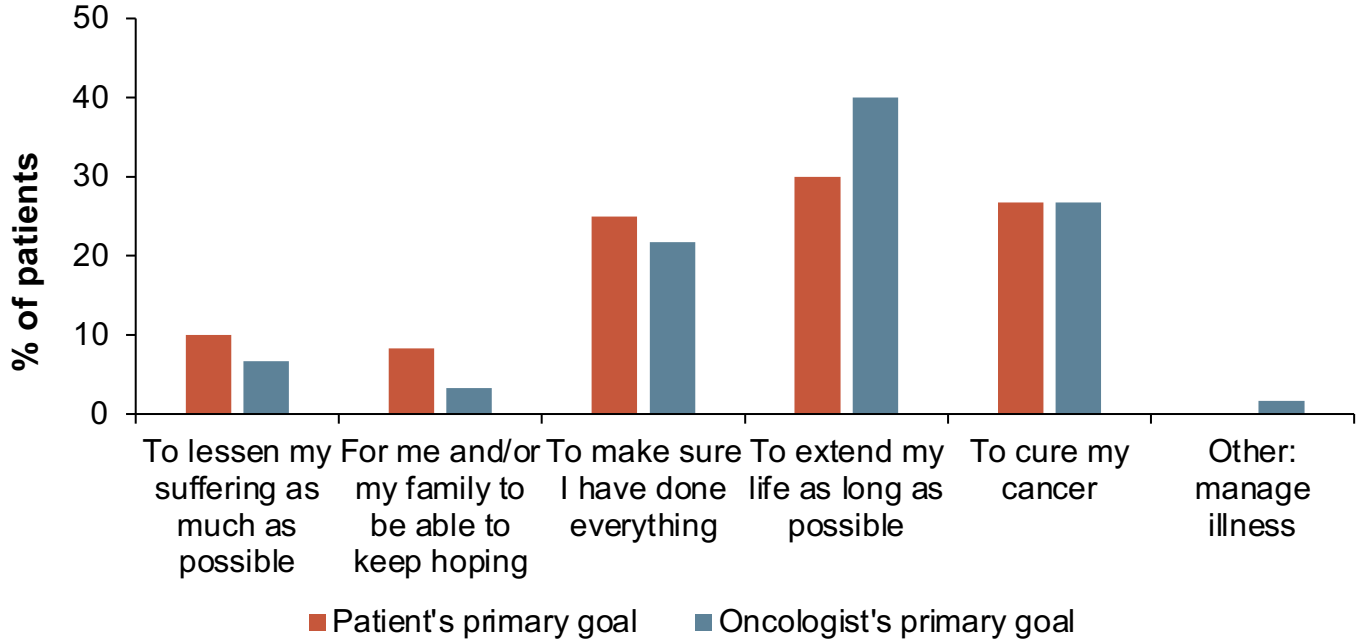
GEP-NET, gastroenteropancreatic neuroendocrine tumour; (p)NET, (pancreatic) neuroendocrine tumour; TKI, tyrosine kinase inhibitor

1. Mele C, et al. Front Endocrinol (Lausanne). 2020;11:591501; 2. Laks S, et al. Cancer;2022:128:435-46; 3. Duan H, et al. Oncologist. 2022;27:447-52;
4. Davar J, et al. J Am Coll Cardiol. 2017;69:1288-304

PATIENT-RELATED FACTORS: PATIENT PREFERENCES

Need for improved patient–provider communication and integration of patient preferences in treatment planning and medical decision-making

Patient-defined goals and preferences among adults with advanced NETs[1]



Percentages may not add up to 100% due to rounding.

Primary therapeutic objectives

- Surgery with curative intent[a]
- Tumour stability versus shrinkage
- Survival
- Symptom control
- Urgency
- Patient preferences
- Quality of life

Only 52% of patients have the same treatment goals as their physician[1]

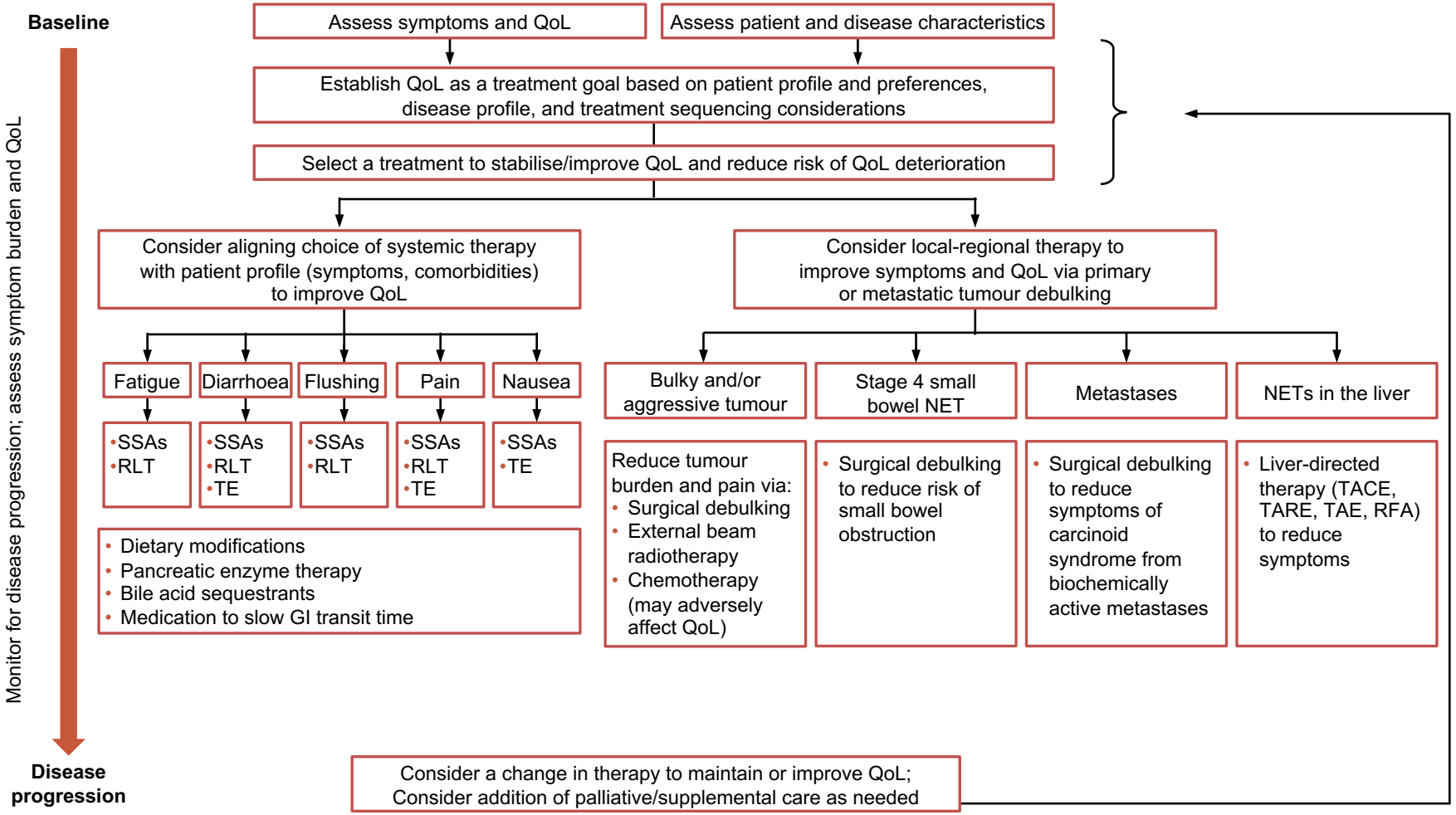
[a] Stage IV is not thought to be curable, even if resectable

NET, neuroendocrine tumour

Li D, et al. J Natl Compr Canc Netw. 2022;20:1330-37.e3

PATIENT-RELATED FACTORS: QUALITY OF LIFE (QOL)

Using QoL considerations in treatment decisions[1]



- Adults living with NETs strongly value independence over survival[2]
- Maintaining current ability to do daily activities is the most important outcome for 47% of patients[2]
- Only 12% of patients consider eliminating symptoms to be the most important outcome[2]

NET, neuroendocrine tumour; QoL, quality of life; RFA, radiofrequency ablation; RLT, radioligand therapy; SSA, somatostatin analogue; TACE, transarterial chemoembolization; TAE, transarterial embolization; TARE, transarterial radioembolization; TE, telotristat ethyl

1. Naraev BG, et al. Expert Rev Anticancer Ther. 2023;23:601-15; 2. Li D, et al. J Natl Compr Canc Netw 2022;20:1330-37.e3

PATIENT-RELATED FACTORS: QUALITY OF LIFE (QOL) EVIDENCE GAPS

Additional work needed to address evidence gaps in GEP-NET treatment and patient QoL

Few direct QoL comparisons between treatment modalities for GEP-NETs; lack of data guiding the optimal sequence of treatments
Few trials provide information on the effects of treatment on patient QoL
Longitudinal data regarding treatment effects on QoL are sparse
PRO assessments of QoL are not used in routine clinical practice
QoL assessment tools are NET-specific
Lack of data supporting the role of hormonal control in maintenance of QoL in patients with GEP-NETs
Role of interventions beyond medical treatments in supporting the physical, emotional, social, and financial well-being of patients with NETs

GEP-NET, gastroenteropancreatic neuroendocrine tumour; NET, neuroendocrine tumour; PRO, patient-reported outcome; QoL, quality of life

Naraev BG, et al. Expert Rev Anticancer Ther. 2023;23:601-15

TREATMENT-RELATED FACTORS

THERAPEUTIC OPTIONS: LIVER-DIRECTED THERAPY

- Limited metastatic disease (liver-directed interventions)
  - Liver metastases resection/destruction/debulking, percutaneous thermal ablation[1]
  - Trans-arterial chemoembolization (TACE)/embolization (TAE)[1]
  - Selective internal radiation therapy (SIRT)[2]
  - Liver transplantation

Clinical indications and contraindications of the main liver-directed therapy procedures for neuroendocrine metastasis treatment, including interventional radiology and nuclear medicine options[3]

Treatment	Main indications	Contraindications	Advantages	Disadvantages
• Percutaneous ablation	• Oligo-metastatic disease (less than 3-5 metastases) • Oligo-progressive disease (1-2 metastases not responding to systemic treatments)	• Irreversible coagulative disorders • Contraindications to sedation or general anaesthesia • Bilio-enteric anastomosis/history of sphincterotomy • Dilatation of intra-hepatic biliary tree due to biliary strictures • Cardiac arrythmia in case of electroporation	• Minimally invasive • Relative fast post-operative recovering phase • Can be repeated	• Useful for a limited burden of disease only
• Transarterial embolization (TAE) • Transarterial chemoembolization (TACE)	• Unresectable hepatic metastatic disease or not suitable for thermal ablation • Disease progression or persistent symptoms despite cold somatostatin analogues therapy	• Portal vein thrombosis • Bilio-enteric anastomosis/history of sphincterotomy • Liver involvement >75% • Impaired hepatic function (bilirubin level 3 mg/dL, ascites) • Allergy to contrast media • Irreversible coagulative disorders	• Treat a large and diffuse disease • Can be repeated • TACE provides a combined ischemic and chemotherapy effect on large and/or diffuse disease	• Frequent post-embolisation syndrome • TAE provides an ischemic effect only • Needs 6-12 h of in-bed stay after treatment due to the arterial femoral access
• Selective Internal Radiation Therapy (SIRT) or radioembolization		• Pre-existing liver disease, including patients who have previously received chemotherapies • Impaired hepatic function (bilirubin level ≥3 mg/dL, ascites) • Greater than 20% lung shunting of the hepatic artery blood flow determined during the work-up • Pre-assessment angiogram that demonstrates abnormal vascular anatomy that would result in significant reflux of hepatic arterial blood to the stomach, pancreas, or bowel	• Better tolerance profile compared with TAE and TACE	• Needs two separate vascular procedures (work-up and treatment) • Needs 6-12 h of in-bed stay after treatment due to the arterial each femoral access • Needs well-organised institutional protocols

h, hours; NET, neuroendocrine tumour

1. Liu DM, et al. Am J Clin Oncol. 2009;32:200-15; 2. Rajekar H, et al. Int J Hepatol. 2011;2011:404916; 3. Cazzato RL, et al. Cancers (Basel). 2021;13:6368

SUPPORTING CLINICAL STUDIES

EVIDENCE-BASE FOR CONSENSUS ON APPROPRIATE INTERVENTIONS

- SSAs are typically first-line therapy for controlling growth of well-differentiated NETs without poor prognostic factors

Study	Regimen	Patients	Key outcome measure	Key result
PROMID (NCT00171873)[1]	Octreotide LAR vs placebo	Metastatic midgut NETs (n=85)	Median TTP	14.3 vs 6.0 months *HR=0.34; 95% CI, 0.20-0.59; p=0.000072*
CLARINET (NCT00353496)[2]	Lanreotide vs placebo	Locally advanced or metastatic non-functioning pancreatic and intestinal NETs (n=204)	Median PFS	Not reached vs 18 months *HR=0.47; 95% CI, 0.30-0.73; p<0.001*

- Upon progression with first-line SSAs, high-dose lanreotide may prolong PFS and delay the use of subsequent therapies

Study	Regimen	Patients	Key outcome measure	Key results
CLARINET FORTE (NCT02651987)[3]	Lanreotide (single-arm) 120 mg every 14 days	Progressive disease (n=99)	Median PFS	5.6 months in pNETs *95% CI, 5.5–8.3* 8.3 months in midgut NETs *95% CI, 5.6-11,1* PFS longer if Ki67 <10%

CI, confidence interval; HR, hazard ratio; Ki67, antigen Kiel 67; LAR, long-acting release; (p)NET, (pancreatic) neuroendocrine tumour; PFS, progression-free survival; SSA, somatostatin analogue; TTP, time to progression

1. Rinke A, et al. J Clin Oncol. 2009;27:4656-63; 2. Caplin ME, et al. N Engl J Med. 2014;371:224-33; 3. Pavel M, et al. Eur J Cancer. 2021;157:403-14

SUPPORTING CLINICAL STUDIES

EVIDENCE-BASE FOR CONSENSUS ON APPROPRIATE INTERVENTIONS

- For patients with SSTR-positive GEP-NETs, PRRT using ^{177}Lu-DOTATATE offers disease control and survival benefit

Study	Regimen	Patients	Key outcome measure(s)	Key result(s)
NETTER-1 (NCT01578239)[1,2]	^{177}Lu-DOTATATE plus best supportive care (including octreotide LAR 30 mg/month) vs high-dose octreotide LAR (60 mg/month)	Advanced midgut NETs (n=229)	Median PFS	Not reached vs 8.4 months *HR=0.21; 95% CI, 0.13-0.33; p<0.001*
			Median OS	48.0 vs 36.3 months *HR=0.84; 95% CI, 0.60-1.17; p=0.3*

- CAP-TEM is recommended in advanced pNETs for which cytotoxic agents are indicated[3]

Study	Regimen	Patients	Key outcome measure	Key result
Phase 2 (NCT01824875)[3]	CAP-TEM vs temozolomide	Progressive, unresectable low or intermediate grade pNETs (n=144)	Median PFS	22.7 vs 14.4 months *HR=0.58; 95% CI, 0.36-0.93; p=0.022*

[a] G2/3, Ki-67 10-55%

^{177}Lu, lutetium-177; CAPTEM, capecitabine plus temozolomide; CI, confidence interval; G, grade; GEP-NET, gastroenteropancreatic neuroendocrine tumour; HR, hazard ratio; Ki67, antigen Kiel 67; LAR, long-acting release; OS, overall survival; PFS, progression-free survival; p(NET), (pancreatic) neuroendocrine tumour; PRRT, peptide receptor radionuclide therapy; SSA, somatostatin analogue; SSTR, somatostatin receptor

1. Strosberg J, et al. N Engl J Med. 2017;376:125-35; 2. Strosberg JR, et al. Lancet Oncol. 20231;22:1752-63; 3. Kunz PL, et al. J Clin Oncol. 2023;41:1359-69

SUPPORTING CLINICAL STUDIES

EVIDENCE-BASE FOR CONSENSUS ON APPROPRIATE INTERVENTIONS

- Everolimus offers PFS improvements for people living with pNETs and non-functional NETs of gastrointestinal, lung, or unknown primary origin

Study	Regimen	Patients	Key outcome measure	Key result
RADIANT-3 (NCT00510068)[1]	Everolimus vs placebo	Advanced, progressive pNETs (n=410)	Median PFS	11.0 vs 4.6 months *HR=0.35; 95% CI, 0.27-0.45; p<0.001*
RADIANT-4 (NCT01524783)[2]	Everolimus vs placebo	Progressive, nonfunctional lung or GI NETs (n=302)	Median PFS	11.0 vs 3.9 months *HR=0.48; 95% CI, 0.35-0.67; p<0.00001*

- Sunitinib is used to treat unresectable metastatic progressive pNETs

Study	Regimen	Patients	Key outcome measure	Key result
Phase 3 (NCT00428597)[3]	Sunitinib vs placebo	Advanced, well-differentiated pNETs (n=171)	Median PFS	11.4 vs 5.5 months *HR=0.42; 95% CI, 0.26-0.66; p<0.001*

CI, confidence interval; G, grade; GI, gastrointestinal; HR, hazard ratio; PFS, progression-free survival; (p)NET, (pancreatic) neuroendocrine tumour

1. Yao JC, et al. N Engl J Med. 2011;364:514-23; 2. Yao JC, et al. Lancet. 2016;387:968-77; 3. Raymond E, et al. N Engl J Med. 2011;364:501-13

TREATMENT-SPECIFIC ISSUES: COMMON ADVERSE REACTIONS

- SSAs
  - Octreotide LAR depot (≥20% of patients): Back pain, fatigue, headache, abdominal pain, nausea, dizziness[1]
  - Lanreotide depot (>10% of patients): Abdominal pain, musculoskeletal pain, vomiting, headache, injection site reaction, hyperglycaemia, hypertension, cholelithiasis[2]
- ^{177}Lu-DOTATATE
  - Thrombocytopenia, lymphopenia, anaemia, pancytopenia, decreased appetite, nausea, vomiting, fatigue (≥10% of patients)[3]
- Everolimus
  - Stomatitis, infections, rash, fatigue, diarrhoea, oedema, abdominal pain, nausea, fever, asthenia, cough, headache, decreased appetite (≥30% of patients)[4]
- Sunitinib
  - Fatigue/asthenia, diarrhoea, mucositis/stomatitis, nausea, decreased appetite/anorexia, vomiting, abdominal pain, hand-foot syndrome, hypertension, bleeding events, dysgeusia/altered taste, dyspepsia, thrombocytopenia (≥25% of patients)[5]
- Expected cumulative toxicity
  - Impact of concomitant medication and/or NET-specific treatment(s)
  - Real-world studies with long follow-up are needed to evaluate the risk of cumulative toxicities of different treatments and treatment sequences,[6] e.g. myelotoxicity (including therapy-related myeloid neoplasms) due to cumulative effects of PRRT and chemotherapies

^{177}Lu, lutetium-177; LAR, long-acting release; NET, neuroendocrine tumour; PPRT, peptide receptor radionuclide therapy; SSA, somatostatin analogue

Package Inserts/Summary of Product Characteristics available at:
1. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/021008s043lbl.pdf; 2. https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/022074s011lbl.pdf;
3. https://www.ema.europa.eu/en/documents/product-information/lutathera-epar-product-information_en.pdf;
4. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022334s016lbl.pdf; 5. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021938s033lbl.pdf (accessed May 2024); 6. Perrier M, et al. Ther Adv Med Oncol. 2023;15:17588359231171041

CLINICAL STUDIES OF ADDITIONAL INTEREST

- Emerging prospective data suggest that ^{177}Lu-based PRRT has activity in advanced pancreatic NETs, and as up-front therapy in G2/3 GEP-NETs

Study	Regimen	Patients	Key outcome measure(s)	Key result(s)
NETTER-2 (NCT03972488)[1]	^{177}Lu-DOTATATE plus octreotide LAR 30 mg/month vs high-dose octreotide LAR (60 mg/month) (first-line)	SSTR-positive, high-proliferation[a] GEP-NETs (n=226)	ORR Median PFS	43.0% vs 9.3% *OR=7.81; 95% CI, 3.32-18.4; p<0.0001* 22.8 vs 8.5 months *HR=0.276; 95% CI, 0.182-0.418; p<0.0001*
OCLURANDOM (EudraCT 2013-004032-30)[2]	^{177}Lu-Octreotate vs sunitinib	Progressive advanced pNETs (n=84)	Median PFS	20.7 (*90% CI,* 17.2-23.7) vs 11 (*90% CI, 8.8-12.4*) months

[a] G2/3, Ki-67 10-55%

^{177}Lu, lutetium-177; CI, confidence interval; G, grade; GEP-NET, gastroenteropancreatic neuroendocrine tumour; HR, hazard ratio; Ki67, antigen Kiel 67; LAR, long-acting release; OS, overall survival; 177Lu, lutetium-177PF; S, progression-free survival; p(NET), (pancreatic) neuroendocrine tumour; PRRT, peptide receptor radionuclide therapy; SSA, somatostatin analogue; SSTR, somatostatin receptor

1. Singh S, et al. J Clin Oncol. 2024;42 (no. 3_Suppl):LBA588; 2. Baudin E, et al. Ann Oncol. 2022;33 (supplement 7):S954 (abstract 887O)

CLINICAL STUDIES OF ADDITIONAL INTEREST

- Sequencing: streptozotocin and everolimus in pNETs

Study	Regimen	Patients	Key outcome measure(s)	Key result(s)
SEQTOR (NCT02246127)[1]	Everolimus followed by streptozotocin upon progression vs the reverse sequence	Advanced G1/2 pNETs, ECOG 0-2 (n=141)	Median PFS ORR	21.5 (*95% CI, 16.9-31.3)* vs 23.8 months *(95% CI, 13.6-30.8) p=0.351* 11% vs 30% *p=0.014*

- Cabozantinib for people living with previously treated, progressive NET

Study	Regimen	Patients	Key outcome measure	Key result
CABINET (NCT03375320)[2]	Cabozantinib vs placebo	Locally advanced or metastatic well or moderately differentiated epNETs (n=197) or pNETs (n=93)	Median PFS	8.2 vs 3.2 months in epNETs *HR=0.41; 95% CI, 0.27-0.62; p<0.0001* 13.7 vs 3.0 months in pNETs *HR=0.25; 95% CI, 0.12-0.49; p<0.0001*

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; epNET, extrapancreatic neuroendocrine tumour; G, grade; HR, hazard ratio; ORR, overall response rate; PFS, progression-free survival; (p)NET, (pancreatic) neuroendocrine tumour

1. Salazar R, et al. Ann Oncol. 2022;33 (suppl_7):S808-69; 2. Chan J, et al. Ann Oncol. 2023;34 (supplement 2):S1292

CLINICAL STUDIES OF ADDITIONAL INTEREST

- Surufatinib in advanced epNETs and pNETs

Study	Regimen	Patients	Key outcome measure	Key result
SANET-ep (NCT02588170)[1]	Surufatinib vs placebo	Unresectable or metastatic, well differentiated epNETs, ECOG 0-1 (n=198)	Median PFS	9.2 vs 3.8 months *HR=0.33; 95% CI, 0.22-0.50; p<0.0001*
SANET-p (NCT02589821)[2]	Surufatinib vs placebo	Progressive, advanced, well differentiated pNETs, ECOG 0-1 (n=172)	Median PFS	10.9 vs 3.7 months *HR=0.49; 95% CI, 0.32-0.76; p=0.0011*

- Levatinib in previously treated advanced GEP-NETs

Study	Regimen	Patients	Key outcome measure	Key result
TALENT (NCT02678780)[3]	Levatinib (open-label)	Advanced G1/2 pNETs or GI-NETs, progression after treatment (n=111)	ORR	29.9% (95% CI, 21.6-39.6) 44.2% in pNETs 16.4% in GI-NETs

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; epNET, extrapancreatic neuroendocrine tumour; G, grade; GEP-NET, gastroenteropancreatic neuroendocrine tumour; GI, gastrointestinal; HR, hazard ratio; ORR, overall response rate; PFS, progression-free survival; (p)NET, (pancreatic) neuroendocrine tumour

1. Xu J, et al. Lancet Oncol. 2020;21:1500-12; 2. Xu J, et al. Lancet Oncol. 2020;21:1489-99; 3. Capdevila J, et al. J Clin Oncol. 2021;39:2304-12

SUMMARY

FACTORS INFLUENCING CHOICE OF GEP-NET THERAPY

INVOLVEMENT OF A MULTIDISCIPLINARY TEAM IS KEY

Tumour	Patient	Provider/treatment
Liver tumour burden (% involvement, size, #, distribution)	Co-morbidities (e.g. bilirubin, Cr, hypertension, diabetes)	Provider preference
Extent of extrahepatic disease	Prior therapy (including Whipple)	Provider experience
Rate of growth/Ki67	Logistics (co-pays, travel)	Availability of therapy
Portal vein patency	Symptoms (hormones, bulk)	Strength of data
Primary tumour site (e.g. pancreas vs SB vs other)	Goals of therapy (stability vs shrinkage) & urgency	
SSTR expression	Concurrent medications	
+/- molecular features		
Overall burden of disease (low volume vs bulky)		

CR, creatinine; GEP-NET, gastroenteropancreatic neuroendocrine tumour; Ki67, antigen Kiel 67; SB, small bowel; SSTR, somatostatin receptor

Courtesy of Dr E. Bergsland

CHALLENGES AND UNMET NEEDS

- Improved patient–provider communication and integration of patient preferences in treatment planning and medical decision-making
- Guidelines vary in terms of level of detail, often recommending several options for a given line of therapy
- Reliable, cost-effective biomarkers for diagnostic accuracy, therapeutic guidance, and early relapse detection
- Reliable tools to assess extent of disease and treatment outcomes
- Individualization of treatment accounting for both tumour- and patient-related factors
- Definitive studies addressing therapeutic sequencing
- Additional tools to support therapeutic decision-making and drug development in NETs, such as those based on tumour growth rate (TGR) kinetics

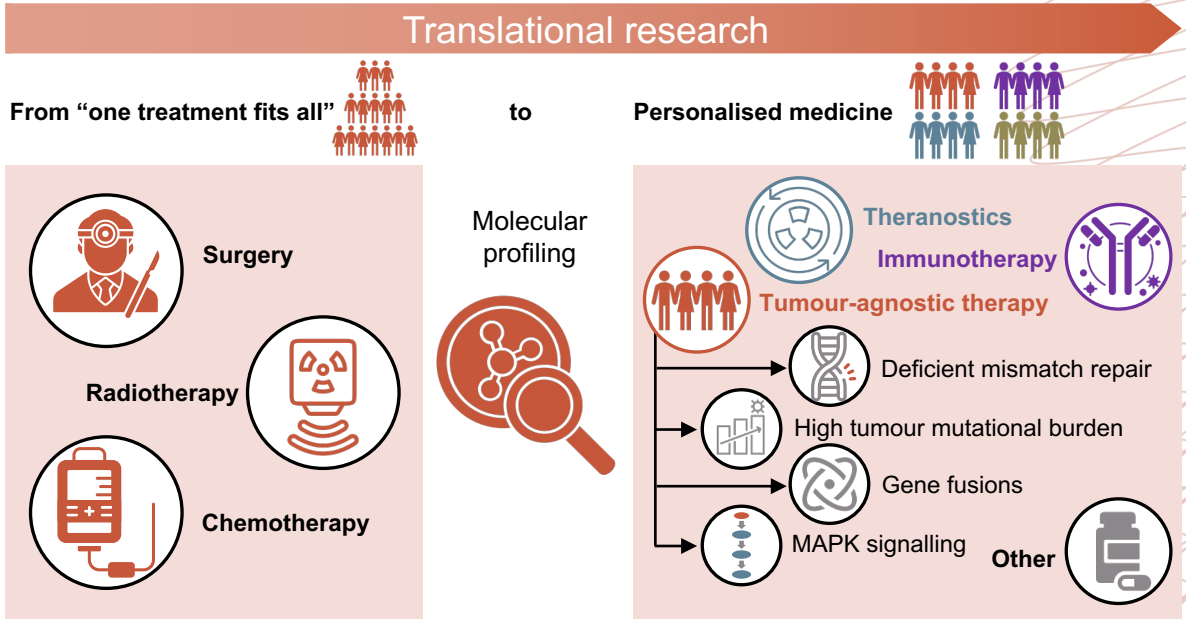


Image adapted from Garcia-Carbonero R, et al. Endocr Rev. 2023;44:724-36

SUMMARY

- Therapeutic choice is based on a number of tumour-, patient-, and treatment-related factors, in the absence of validated predictive biomarkers (efficacy) or clinical trials addressing sequence of therapy
- Involvement of a multidisciplinary team is essential
- In addition, communication between patients and HCPs is needed to ensure that patient preferences are incorporated into decision-making and treatment plans
- Ultimately, choice of treatment strategy needs to integrate efficacy, QoL, and both short- and long-term toxicity

HCP, healthcare practitioner; QoL, quality of life

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