Optimizing the management of gastroenteropancreatic neuroendocrine tumours

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Reviewing the evidence base for GEP-NETs: What is new in 2021?

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What is the current treatment landscape in GEP-NETs?

GEP-NET clinical management: Current therapy options[1–3]

SSAs
(octreotide, lanreotide)
+
symptomatic control

+

Midgut NET

Hepatic arterial embolization
liver-dominant

PRRT (^{177}Lu-DOTATATE)
Extrahepatic, strong somatostatin receptor expression

mTOR inhibitor (everolimus)
Extrahepatic, weak somatostatin receptor expression

Non-midgut GI/lung NET

- **Chemotherapy** (capecitabine/temozolomide)
  Relatively aggressive, foregut (lung/stomach/thymus)
- **mTOR inhibitor** (everolimus)
  Extrahepatic, weak somatostatin receptor expression
- **PRRT** (^{177}Lu-DOTATATE)
  With positive somatostatin receptor expression

Pancreatic NET

- **Chemotherapy** (capecitabine/temozolomide)
- **Multi-receptor TKIs** (sunitinib: VEGFR, PDGFR, KIT)
- **mTOR inhibitor** (everolimus)
  Extrahepatic, weak somatostatin receptor expression

^{177}Lu-DOTATATE, ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate; GEP-NET, gastroenteropancreatic neuroendocrine tumour; GI, gastrointestinal; mTOR, mechanistic target of rapamycin; NET, neuroendocrine tumour; PDFGR, platelet-derived growth factor receptor; PRRT, peptide receptor radionuclide therapy; SSAs, somatostatin analogues; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor.

1. Uri I, Grozinsky-Glasberg S. *Clin Diabetes Endocrinol.* 2018;4:16; 2. Pavel M, et al. *Ann Oncol.* 2020;31:844; 3. Herrera-Martinez AD, et al. *Drugs* 2019;79:21–42.

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How are advances in our understanding of the molecular pathology of GEP-NETs shaping future treatment prospects?

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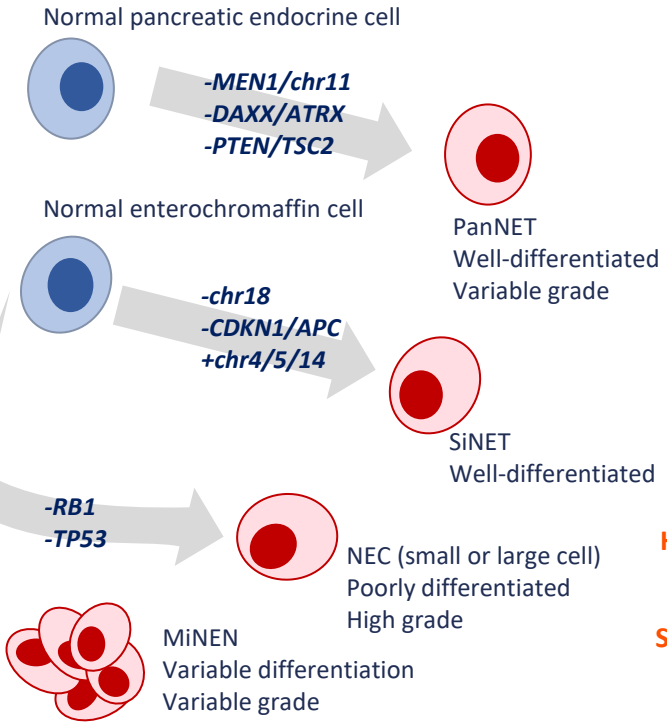
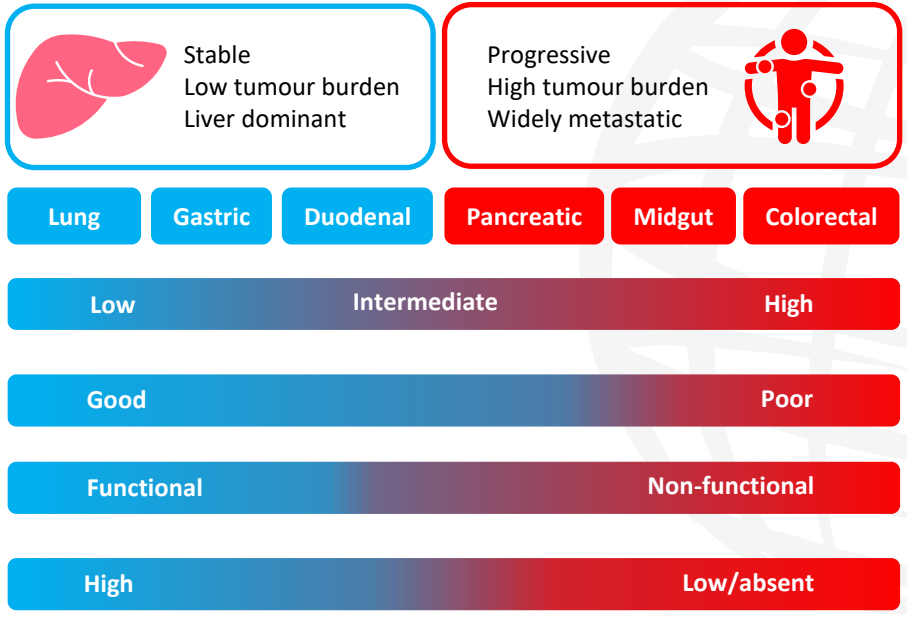
Revised classification and heterogeneity of GEP-NETs

Fairly limited pathogenesis of NETs and NECs[1,2]



High disease heterogeneity[3]



GEP-NET, gastroenteropancreatic neuroendocrine tumour; MiNEN, mixed neuroendocrine/non-neuroendocrine neoplasm; NEC, neuroendocrine carcinoma; NET, neuroendocrine tumour; PanNET, pancreatic NET; SiNET, small intestinal NET; SSTR, somatostatin receptor.

1. Nagetegaal ID, et al. *Histopathology.* 2020;76:182–8; 2. Maffacini A, Carpa A. *Endocrine Rev.* 2019;40:506–36; 3. Information supplied by Prof. Strosberg.

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What treatment options are on the horizon for GEP-NETs?

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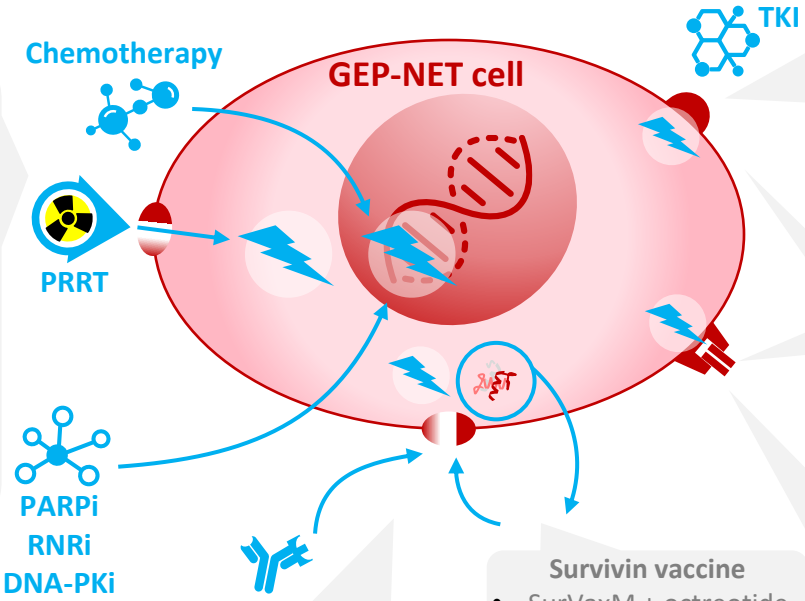
Emerging therapies for GEP-NETs

Novel PRRT combination therapies

- **PRRT + chemotherapy**
  ^{177}Lu-DOTATATE + CAPTEM (NCT04194125, NCT02358356)
- **PRRT + PARPi**
  ^{177}Lu-DOTATATE + olaparib (NCT04086485)
- **PRRT + RNRi**
  ^{177}Lu-DOTATATE + triapine (NCT04234568)
- **PRRT + DNA-PKi**
  ^{177}Lu-DOTATATE + peposertib (NCT04750954)



TKI monotherapy

- **VEGFR multi-kinase inhibitors**
  Surufatinib (NCT02589821, NCT02588170)
  Axitinib (NCT01435122)
  Lenvatinib (NCT02678780)
  Cabozantinib (NCT01466036)
  Pazopanib (NCT01841736)

Immunotherapy/VEGF inhibitor combination

- Bevacizumab + atezolizumab (NCT03074513)

Immunotherapy

- **PD-1/PD-L1 axis**
  Durvalumab + tremelimumab (NCT03095274)
  Nivolumab + temozolomide (NCT03728361)
  Spartalizumab (NCT02955069)
- Nivolumab + ipilimumab (NCT03420521)

Survivin vaccine

- SurVaxM + octreotide (NCT03879694)

SSTR bispecific antibodies

- (NCT03411915)

Somatostatin receptor
VEGF receptor
PD-1/PD-L1 axis
Survivin

^{177}Lu-DOTATATE, ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate; CAPTEM, capecitabine + temozolomide; DNA-PKi, DNA-dependent protein kinase inhibitor; GEP-NET, gastroenteropancreatic neuroendocrine tumour; PARPi, PARP, poly (adenosine diphosphate-ribose) polymerase inhibitor; PD-1, programmed cell death-1; PD-L1, programmed cell death ligand-1; PRRT, peptide receptor radionuclide therapy; RNRi, ribonucleotide reductase inhibitor; SSTR, somatostatin receptor; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor.

Das S, Dasari A. *Ther Adv Med Oncol.* 2021;13:1–15.

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How safe and effective are emerging treatment options in GEP-NETs?

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Emerging treatments in GEP-NETs: Safety and efficacy profiles

PRRT + chemotherapy combinations

^{177}Lu-DOTATATE + CAPTEM (NCT02358356)

- SiNET:
  ORR 31%, median 15-month PFS 90%
- PanNET:
  ORR 68%, 12-month PFS 76%
- G3: 75% (SiNET)
  and 28% (PanNET)

^{177}Lu-Edotreotide + everolimus

- 10/11 patients had GEP-NET
- ORR 9%, mPFS 23.3 months
- G3: 36%
  (infection, fatigue, pneumonitis, neutropenia)

Targeted TKI therapies

	Pancreatic	Extrapancreatic
Surufatinib • NCT02589821 • NCT02588170	mPFS 10.9 months G3/4: hypertension 38%, proteinuria 10%	mPFS 9.2 months G3/4: hypertension 36%, proteinuria 19%
Axitinib • NCT01435122	Extrapancreatic ORR 3%, mPFS 26.7 months G3/4: hypertension 63%	
Lenvatinib • NCT02678780	Pancreatic: ORR 42.3%, mPFS 15 months Gastrointestinal: ORR 16.4%, mPFS 15.4 months G3/4: hypertension 22%, fatigue 11%, diarrhoea 11%	
Cabozantinib • NCT01466036	Pancreatic: ORR 15%, mPFS 21.8 months Extrapancreatic: ORR 15%, mPFS 31.4 months G3/4: hypertension 13%, hypophosphatemia 10%, diarrhoea 10%	
Pazopanib • NCT01841736	Extrapancreatic ORR 2.1%, mPFS 11.6 months G3/4: hypertension 26.9%, increased transaminase 18%	

^{177}Lu-DOTATATE, ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate; CAPTEM, capecitabine + temozolomide; G3/4, Grade 3/4 adverse events; neuroendocrine tumour; GEP-NET, gastroenteropancreatic neuroendocrine tumour; mPFS, median progression-free survival; ORR, overall response rate; PanNET, pancreatic neuroendocrine tumour; PFS, progression-free survival; PRRT, peptide receptor radionuclide therapy; SiNET, small intestinal NET; TKI, tyrosine kinase inhibitor.

Das S, Dasari A. *Ther Adv Med Oncol.* 2021;13:1–15.

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The impact of new data: Do we need to change our practice?

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Can we improve on the clinical outcomes achieved with current treatment approaches in GEP-NETS?

Treatment goals and optimizing clinical outcomes in GEP-NETs

Prolonging OS without increasing toxicity remains the ultimate treatment goal

Survival rates

Swedish registry study[1]

N=811

Surgery and SSA most common first-line therapy

46% received SSA second-line after first-line surgery

mOS from diagnosis

Si-NET: 7 years (95% CI 6.20–NR)

Pan-NET: 4.3 years (95% CI 2.8–NR)

5-year survival rate 63%

Clinical outcomes and safety

Australian tertiary cancer centre[2]

^{177}Lu-DOTATATE PRRT

N=123

51 months follow-up

mOS: 61 months (95% CI 54.2–67.8)

mPFS: 34.2 months (95% CI 30.3–38.17)

Acute leukaemia: 2.4%

Western Australia long-term follow-up[3]

Lutetium octreotate PRRT

N=104

68 months follow-up

mOS: 71 months (95% CI NS)

10-year

OS: 30.1%

PFS: 29.3%

MDS/leukaemia: 6.7%

PRRT shown to be effective in relieving symptoms of NETs in both carcinoid syndrome and functional Pan-NETs[4–6]

CI, confidence interval; GEP, gastroenteropancreatic; m, median; MDS, myelodysplastic syndrome; NET, neuroendocrine tumour; NR, not reached; NS, not specified; OS, overall survival; Pan, pancreatic; PFS, progression-free survival; PRRT, peptide receptor radionuclide therapy; Si, small intestine; SSA, somatostatin analogue.

1. Lesen E, et al. *J Cancer.* 2019;10:6876–87; 2. Nalder M, et al. *J Clin Oncol.* 2021;39(Suppl. 15)e16198; 3. Kennedy KR, et al. *J Clin Oncol.* 2021;39(Suppl. 15):e16202; 4. Zandee WT, et al. *J Clin Endocrinol Metabol.*2021; DOI:10.1210/clinem/dgab289 [online ahead of print]; 5. Strosberg J, et al. *J Clin Oncol.* 2018;36:2578–84; 6. Uri I, Grozinsky-Glasberg S. *Clin Diabetes Endocrinol.* 2018;4:16.

What advances have been made in PRRT treatment for GEP-NETs?

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Evolving role of PRRT in GEP-NETs

Study	Setting	PRRT regimen	Clinical outcome(s)	Safety
5-year long-term outcomes				
NETTER-1[1] Phase III RCT	Midgut NETs (N=231)	^{177}Lu-DOTATATE vs high-dose long-acting octreotide*	**Median OS: 48** vs 36.3 months **HR 0.84** (95% CI 0.60–1.17) 5-year survival: 37.1% vs 35.4%	MDS – 1.8% No new cases during follow-up
Use in earlier disease stage				
NETTER-2[2] Phase III RCT *RECRUITING***	High G2/low-G3 GEP-NETs (N=222)	^{177}Lu-DOTATATE vs high-dose / long-acting octreotide	Primary endpoint: PFS through Week 72	
Novel regimens				
COMPETE[3] Phase III RCT *RECRUITING***	Pan-NETs; non-functional GI-NETs (N≈300)	^{177}Lu-DOTATOC vs everolimus	Primary endpoint: PFS up to 30 months	
ETCTN-10388[4,5] Phase I single-arm *RECRUITING***	Well-differentiated GEP-NETs following prior treatment failure (N≈29)	^{177}Lu-DOTATATE + triapine	Primary endpoint: Evaluate recommended Phase II dose	

PRRT combination regimens with drugs other than SSAs remains experimental and are not recommended outside of clinical trials

*__NETTER-1:__ 36.0% (n/N=41/114) of participants in the control arm crossed over to PRRT during long-term follow-up (22.8% of these participants crossed over within 24 months following randomization). 31.0% (n/N=36/114) specifically received ^{177}Lu-DOTATATE. **__NETTER-2; COMPETE; ETCTN-10388:__ Recruitment status correct as of 22 July 2021.

CI, confidence interval; G, grade; GEP, gastroenteropancreatic; GI, gastrointestinal; HR, hazard ratio; m, median; MDS, myelodysplastic syndrome; NET, neuroendocrine tumour; OS, overall survival; Pan, pancreatic; PFS, progression-free survival; PRRT, peptide receptor radionuclide therapy; RCT, randomized controlled trial; SSA, somatostatin analogue..

1. Strosberg JR, et al. *J Clin Oncol.* 2021:39; abstr 4112; 2. NCT03972488. Available at: https://clinicaltrials.gov/ct2/show/NCT03972488 (accessed July 2021); 3. NCT03049189; 4. NCT04234568. NCT information available at https://clinicaltrials.gov/ (accessed July 2021); 5. Chauhan A, et al. *J Clin Oncol.* 2020;38(Suppl. 15):TPS4660.

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What are we learning from real-world experience surrounding clinical management of GEP-NETs?

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Managing GEP-NETs: Real-world insights

Advanced GEP-NETs

SSA use[1]

N=540

Common first-line intervention

Off-label dose modifications reported

- **Lanreotide use more common** (38.7%) vs octreotide use (6.3%)
- **Majority** (85.7%) patients **on index SSA 1.5 years** after initiation

^{177}Lu-DOTATATE use[2]

N=40

Safe and effective in SSTR-positive metastatic GEP-NETs

After 4 treatment cycles (n=26):

- **ORR: 19.2%**
- **DCR: 92.3%**
- **mPFS** (months)**: 27.2**

PRRT in advanced Pan-NETs

NETTER-R Registry[3]

N=110

^{177}Lu-DOTATATE well tolerated with a safety profile consistent with NETTER-1

At 24.5 months' median follow-up:

- **mOS** (months)**: 41.4**
- **71.8% experienced ≤1 TEAE:**
  - Nausea – 28.2%
  - Fatigue – 22.7%

No MDS/AML reported during follow-up

Emerging combination regimens

ECOG-ACRIN (E2211)[4]

N=144

TEM vs **CAPTEM**-based regimens in advanced Pan-NETs

At 29 months' median follow-up:

- **mOS** (months)**: 38.0** vs **NR**
- **mPFS** (months)**: 14.4** vs **22.7**

Risk of severe PRRT-related haematological toxicity is small but not insignificant

t-MN (MDS/AML) incidence reportedly ranges from 1.8[5,6]–2.61%[7]

AML, acute myeloid leukaemia; CAPTEM, capecitabine plus temozolomide; CI, confidence interval; DCR, disease-control rate; GEP, gastroenteropancreatic; m, median; MDS, myelodysplastic syndrome; NET, neuroendocrine tumour; NR, not reached; ORR, objective response rate; OS, overall survival; Pan, pancreatic; PFS, progression-free survival; PRRT, peptide receptor radionuclide therapy; SSA, somatostatin analogue; SSTR, somatostatin receptor; TEAE, treatment-emergent adverse event; TEM, temozolomide; t-MN, therapy-related myeloid neoplasm.

1. Klink AJ, et al. *The Oncologist.* 2019;24:1331–39; 2. Casas EAJ, et al. *J Clin Oncol.* 2021;39(Suppl. 3):364; 3. Clement D, et al. *J Clin Oncol.* 2021;39(Suppl. 15): 4116; 4. Kunz PL, et al. *J Clin Oncol.* 2018;36(Suppl. 15):4004; 5. Chantadisai M, et al. *Eur J Nucl Med Mol Imaging.* 2021;48:1390–8; 6. Strosberg JR, et al. *J Clin Oncol.* 2021;39(Suppl. 15):4112; 7. Sonbol MB, et al. *JAMA Oncol.* 2020;6:1086–92.

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How do PRRT approaches compare with molecularly targeted therapies in terms of optimizing outcomes for patients with GEP-NETs?

Navigating an increasingly complex treatment landscape

Study	Population	Regimen	Key clinical outcomes
SUN1111[1] Phase III RCT	**Pan-NETs (N=171)**	**Sunitinib** Placebo	**ORR: 9.3%** vs 0% p<0.007 **mPFS: 11.4** vs 5.4 months; HR 0.42 p<0.001
SANET-P[2] Phase III RCT	**Pan-NETs (N=172)**	**Surufatinib** Placebo	**mPFS 10.9** vs 3.7 months; HR 0.49 p=0.0011
SANET-EP[3] Phase III RCT	**Extra-Pan-NETs (N=198)**	**Surufatinib** Placebo	**mPFS: 9.2** vs 3.8 months; HR 0.33 p<0.0001
AXINET[4] Phase III RCT	**Extra-Pan-NETs (N=256)**	**Axitinib/octreotide** Placebo/octreotide	**ORR: 17.5%** vs 3.8% p<0.0004 **mPFS: 17.2** vs 12.3 months; HR 0.82 p=0.169
Alliance A021202[5] Phase II RCT	**Extra-Pan-NETs (N=171)**	**Pazopanib** Placebo	**mOS: 41** vs 42 months; HR 1.13 p=0.70 **mPFS: 11.6** vs 8.5 months; HR 0.53 p<0.0005
TALENT[6] Phase II single-arm	**G1 or G2 Pan-NET; GI-NET progressed on SSA (N=111)**	**Lenvatinib**	**ORR: Overall – 29.9%; Pan-NET – 44.2%; GI-NET – 16.4%**
CABINET[7] Phase III RCT *RECRUITING**	**Advanced NETs progressed on prior therapy**	**Cabozantinib** Placebo	**PFS up to 8 years**

***CABINET:** Recruitment status correct as of July 2021. G, grade; GI, gastrointestinal; HR, hazard ratio; m, median; NET, neuroendocrine tumour; NS, not specified; ORR, objective response rate; OS, overall survival; Pan, pancreatic; PFS, progression-free survival; RCT, randomized controlled trial; SSA, somatostatin analogue.

1. Raymond E, et al. *N Engl J Med.* 2011;364:501–13; 2. Xu J, et al. *Lancet Oncol.* 2020;21:1489–99; 3. Xu J, et al. *Lancet Oncol.* 2020;21:1500–12;
4. Garcia-Carbonero R, et al. *J Clin Oncol.* 2021;39:360; 5. Bergsland E, et al. *J Clin Oncol.* 2019;37(Suppl. 15):4005; 6. Capdevila J, et al. *J Clin Oncol.* 2021;39:2304–12;
7. NCT03375320. NCT information available at https://clinicaltrials.gov/ (accessed July 2021).

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What more is needed to optimize outcomes for our patients with GEP-NETs, particularly in terms of survivorship and quality of life?

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Overcoming unmet needs in the GEP-NETs community

New and emerging therapies may help optimize clinical outcomes and maximize QoL[1,2]

NETTER-1[2]

PRRT vs SSA

(^{177}Lu-DOTATATE vs high-dose octreotide)

Significant QoL benefit (in addition to PFS benefit)

Significantly prolonged time-to-deterioration of QoL across multiple domains:

- Global health status
- Physical functioning
- Role functioning
- Fatigue
- Pain
- Diarrhoea*
- Disease-related worries

What more is needed?[1,3]

- **Improve differential diagnosis of treatment-related vs disease-related symptoms, notably diarrhoea**
- **Improve utilization of existing resources**
- **Educate HCPs and encourage patient engagement**
- **Provide information and resources to keep patient organization websites up to date**

*Diarrhoea, often ascribed to carcinoid syndrome, is actually often from therapy (SSAs causing steatorrhoea) or from bowel surgery (bile acid malabsorption).[3]

GEP, gastroenteropancreatic; HCPs, healthcare professionals; NET, neuroendocrine tumour; PFS, progression-free survival; PRRT, peptide receptor radionuclide therapy; QoL, quality of life; SSA, somatostatin analogue.

1. Leyden S, et al. *Int J Cancer.* 2020;146:1308–15; 2. Strosberg J, et al. *J Clin Oncol.* 2018;36:2578–84; 3. Eads JR, et al. *Pancreas.* 2020;49:1123–30.

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Progressive disease: How should we monitor and treat our patients?

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What requirements for multidisciplinary treatment and care are needed to optimize disease management?

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Multidisciplinary care underpins personalized treatment

Medical oncologist
co-ordinate treatment and care decisions

Radiologist
radiological imaging and disease staging

Pathologist
accurate histological and molecular tumour profile

Social worker
psychosocial support

Nuclear medicine specialist
expertise in radiopharmaceutical treatments

Radiation oncologist
radiotherapy expertise

Surgical oncologist
surgical expertise

Genetic counsellor
familial impacts of hereditary disease

Nutritionist
dietary support

Endocrinologist
symptom control and monitoring

Nurse specialist
ongoing care and follow-up

Each patient should be individually assessed and discussed by a dedicated multidisciplinary team comprising experts in the management of NETs[1–3]

NET, neuroendocrine tumour.

1. NCCN. 2018. NCCN Guidelines for Patients: Neuroendocrine Tumours. Available at www.nccn.org/patients/guidelines/content/PDF/neuroendocrine-patient.pdf (accessed June 2021); 2. Uri I, Grozinsky-Glasberg S. *Clin Diabetes Endocrinol.* 2018;4:16; 3. NANETS. Guidelines Compendium 2020. Available at https://nanets.net/images/2020_Guidelines_Compendium.pdf (accessed June 2021).

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How should we monitor our patients with GEP-NETs to better support clinical and quality of life outcomes?

Close and effective monitoring is imperative to optimize outcomes

General recommendations for follow-up exist but should be tailored to individual patient and disease status[1,2]

Where warranted, follow-up investigations should include:[1,2]

Small localized NETs G1 (<1 cm in size) with origin in the appendix or rectum do not need follow-up if R0-resected and no adverse histological features reported[1]

Clinical symptom monitoring

- Fatigue
- Weight loss

Imaging

- **R0/R1-resected NET G1–G2**:
  CT or MRI every 3–6 months life-long follow-up (ESMO)[1]
  CT or MRI every 12 weeks to 12 months up to 1 year post-resection then every 6–12 months up to 10 years* (NCCN)[2]
- **NEC G3**:
  CT or MRI every 2–3 months (ESMO)[1]
  CT or MRI every 3–6 months for 2 years and every 6–12 months up to 10 years (NCCN)[2]
- Similar staging intervals apply to advanced disease

Staging intervals may be extended 1–2 years with increasing duration of follow-up (depending on tumour biology)[1]

Biomarkers may play a role in functional NETs but no single currently available biomarker is sufficient as a diagnostic, prognostic or predictive marker in patients with NETs[1–3]

*As clinically indicated.

CT, computerized tomography; G, grade; MRI, magnetic resonance imaging; NEC, neuroendocrine carcinoma; NET, neuroendocrine tumour; SSTR, somatostatin receptor.

1. Pavel M, et al. *Ann Oncol.* 2020;31:844; 2. NCCN. 2021. NCCN Guidelines Version 1.2021: Neuroendocrine and Adrenal Tumors [Discussion update in progress]. Available at www.nccn.org/guidelines/category_1 (accessed July 2021); 3. Sansone A, et al. *Cancers (Basel).* 2019;11:1113.

How do we currently assess and define disease progression in GEP-NETS?

Evaluating disease progression relies on appropriate imaging

Morphological and functional imaging are crucial in the clinical management of GEP-NETs[1]

Disease progression viewed within the context of:[2,3]

tumour growth

+

appearance of new lesions

Interpret changes in SUV with caution[1,3]

Comprehensive clinical evaluation is imperative to aid interpretation and fully assess disease status

Recommended imaging modalities[4]

CT	Extrahepatic disease (e.g. thorax, abdomen and pelvis)
MRI	Liver metastases (detection + follow-up) Preferable to avoid radiation exposure especially in younger patients requiring long-term serial imaging
SR-PET	Appearance and/or progression of GEP-NET lesions Follow-up well-differentiated GEP-NETs and metastases, including SSTR-positive
F-FDG-PET	Limited to SSTR-negative NET patients

CT, computerized tomography; F-FDG, ^{18}F-fluoro-D-glucose; GEP, gastroenteropancreatic; MRI, magnetic resonance imaging; NET, neuroendocrine tumour; PET, positron emission tomography; SSTR, somatostatin receptor; SUV, standard uptake value.

1. Garcia-Carbonero R, et al. *Cancer Metastasis Rev.* 2015;34:823–42; 2. Tirkes T, et al. *RadioGraphics.* 2013;33:1323–41;
3. Calabrò D, Argalia G, Ambrosini V. *Diagnostics (Basel).* 2020;10:1059. 4. Merino-Casabiel X, et al. *Clin Transl Oncol.* 2018;20:1522–8.

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How should we manage patients in the event of disease progression in the first-line setting?

Treatment options beyond the first line?

Second-line treatment for advanced NETs depends on location and burden of disease

Multidisciplinary treatment of advanced NETs

Surgery

If resection possible,
consider even in setting of stage IV disease

Nonsurgical liver-directed therapy

Embolization (+/- chemotherapy)

Medical treatment

Cytotoxic chemotherapy
e.g. foregut NETs (pancreatic, lung)

Targeted agents
e.g. GEP-NETs – everolimus; Pan-NETs – sunitinib

PRRT
e.g. GEP-NETs

GEP, gastroenteropancreatic; NET, neuroendocrine tumour; Pan, pancreatic; PRRT, peptide receptor radionuclide therapy.

Reidy, DL. Neuroendocrine tumors. Presented at: 2014 Gastrointestinal Cancers Symposium, San Francisco, 16–18 January, 2014.

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How might emerging treatment options impact clinical management following disease progression in future?

New therapies, new horizons for GEP-NETs

Treatment options for GEP-NETs are expanding, notably in the field of PRRT:[1–5]

Combination therapy with PRRT[1,2]

- Triapine + ^{177}Lu-DOTATATE
- Olaparib + ^{177}Lu-DOTATATE
- Peposertib + ^{177}Lu-DOTATATE
- Chemotherapy + ^{177}Lu-DOTATATE

Novel TKIs (antiangiogenics)[1]

- Surufatinib (adv. NETs)
- Axitinib (extrapancreatic origin)
- Cabozantinib (adv. NETs)
- Pazopanib (adv. Pan-NETs)
- Lenvatinib (carcinoid tumours)
- Famitinib (G1/G2 + adv. GEP-NETs)
- Regorafenib (carcinoid or Pan-NETs)
- Nintedanib (extrapancreatic origin)
- Anlotinib (adv. GEP-NETs)

Novel radioligand theranostics[3–5]

- ^{68}Ga-JR11 + ^{177}Lu-DOTA-JR11 (^{177}Lu-OPS-201)
- ^{177}Lu-Edotreotide; ^{177}Lu-Satoreotide Tetraxetan
- α-, β-, γ-emitting radionuclides
- Membrane-specific antigen/ receptor theranostic approaches e.g. targeting GRPR or CCKR-2
- Intra-arterial administration

The expanding treatment landscape may deliver more effective therapies with fewer treatment burdens to support prolonged survivorship and maximize QoL in future for patients with GEP-NETs[1]

adv., advanced; CCKR-2, cholecystokinin receptor-2; G, grade; GEP, gastroenteropancreatic; GRPR, gastrin-releasing peptide receptor; NET neuroendocrine tumour; Lu, lutetium; Pan, pancreatic; PRRT, peptide receptor radionuclide therapy; QoL, quality of life; TKI, tyrosine kinase inhibitor.

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