

NEUROENDOCRINE NEOPLASMS

GENERAL OVERVIEW AND CLASSIFICATION

- Gastroenteropancreatic neuroendocrine neoplasms (GEP-NEN) are heterogeneous; management is driven by primary site, differentiation, grade/Ki-67, SSTR expression, functional status, tumour burden and pace, and the need for objective response.
- Always distinguish well-differentiated NET from poorly differentiated NEC. A high Ki-67 alone does not define NEC.

WHO classification — treatment-defining distinction

Entity	Differentiation	Ki-67
NET G1	Well differentiated	<3%
NET G2	Well differentiated	3–20%
NET G3	Well differentiated	>20%
NEC, small/large cell	Poorly differentiated	>20%
MinEN	Variable	Variable

WHO classification: grade and differentiation are separate axes

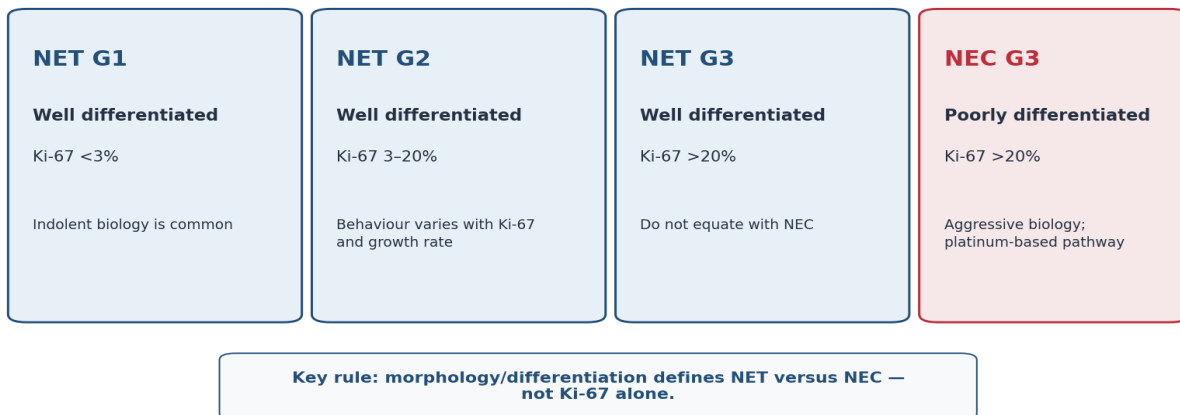


Figure 1. NET G3 remains well differentiated; NEC is poorly differentiated. Ki-67 alone does not define NEC.

UZA PRACTICE POINT

- NET G3 ≠ NEC. Morphology/differentiation is essential. In difficult high-grade cases request expert GI pathology review; p53/Rb abnormalities support NEC, while DAXX/ATRX loss in pancreatic primaries supports NET biology.

Treatment selection — considerations

What drives treatment choice in advanced GEP-NET?

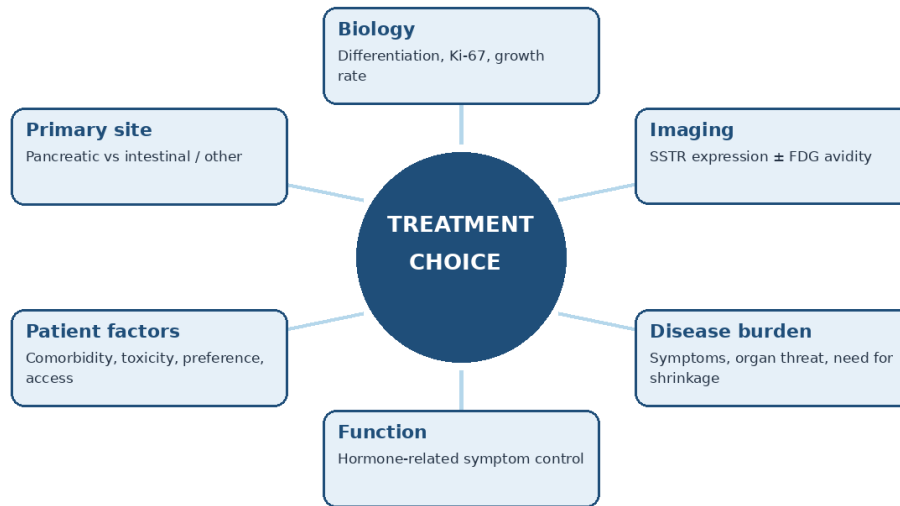


Figure 2. Treatment choice integrates tumour biology, imaging, disease burden, functional symptoms and patient factors.

Initial work-up

- Pathology: morphology/differentiation, Ki-67 in hotspot, mitotic count, synaptophysin/chromogranin; explicitly classify NET G3 versus NEC in high-grade NEN.
- Imaging: multiphasic CT chest/abdomen/pelvis; liver MRI when liver-dominant disease or local treatment is considered; SSTR-PET/CT for well-differentiated advanced NET and before PRRT.
- FDG-PET/CT: consider in NET G3, higher G2, rapidly progressive or heterogeneous disease, and suspected dedifferentiation. Dual SSTR/FDG imaging is particularly useful before PRRT in aggressive disease.
- Biochemistry should be symptom-directed (e.g. 5-HIAA, insulin/C-peptide, gastrin, glucagon, VIP). Chromogranin A has limited specificity and should not be used as a stand-alone diagnostic/response marker.
- Consider germline counselling/testing in pancreatic NET with young age, multifocality, family history or MEN1/VHL/NF1/TSC phenotype.

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LOCALIZED DISEASE AND FOLLOW-UP

Localized well-differentiated NET

Primary	Practical approach
Pancreatic NET	Surgery is curative treatment. Selected asymptomatic non-functional ≤ 2 cm low-risk lesions may undergo active surveillance; >2 cm, functional, growing or higher-risk lesions generally resect.
Small-intestinal NET	Resect primary with mesenteric lymphadenectomy when feasible; assess multifocality, mesenteric fibrosis and vascular involvement. In metastatic disease, resection of an asymptomatic primary is individualized.
Gastric NET	Type 1: usually endoscopic management/surveillance. Type 2: manage gastrinoma/MEN1 plus local lesions. Type 3: more aggressive; oncologic resection according to size, grade and invasion.
Rectal NET	Small low-grade lesions can usually be removed endoscopically. Size, muscularis invasion, lymphovascular invasion and higher grade increase nodal risk and may require radical surgery.

ADJUVANT THERAPY

- There is no established role for routine adjuvant systemic treatment after complete resection of a well-differentiated GEP-NET.

Follow-up after curative-intent treatment

- NET recurrence can occur substantially later than in most gastrointestinal cancers; long-term follow-up is therefore appropriate, individualized by primary site, stage, grade/Ki-67, nodal status and resection status.
- Pancreatic NET tends to recur earlier than small-intestinal NET. Cross-sectional imaging is the backbone; SSTR imaging is not required at every routine visit.

Functional syndromes

Syndrome	First steps / tumour-directed strategy
Carcinoid syndrome	Long-acting SSA. If persistent diarrhoea: optimize dose/interval, exclude alternative causes, consider telotristat; progressive SSTR+ disease may benefit from PRRT.
Insulinoma	Prevent hypoglycaemia (dietary measures, diazoxide). SSA only with caution; everolimus may help via hyperglycaemic effect; PRRT for appropriate SSTR+ metastatic disease.
Gastrinoma / other functional pNET	Control hormone-related syndrome plus tumour-directed treatment according to stage and biology.

CLINICAL PEARL

- Diarrhoea in a NET patient is not automatically carcinoid syndrome. Consider pancreatic exocrine insufficiency (including SSA-related), bile-acid malabsorption, short bowel, bacterial overgrowth and treatment-related causes.
- In clinically significant carcinoid syndrome, assess for carcinoid heart disease (NT-proBNP and echocardiography when indicated).

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ADVANCED WELL-DIFFERENTIATED G1/G2 NET

Central UZA treatment logic

ADVANCED WELL-DIFFERENTIATED GEP-NET	
Assess: SSTR expression • progression • primary site • Ki-67 / FDG phenotype • tumour burden • need for shrinkage	
Clinical situation	Preferred direction
Stable / slow SSTR+ G1 or low-G2 NET	SSA (lanreotide or octreotide); observation only in very selected asymptomatic low-volume stable disease
Progressive SSTR+ GI NET	PRRT is a major preferred option when suitable
Higher G2, especially Ki-67 ≥10%, SSTR+	Consider early PRRT; do not automatically sequence multiple targeted therapies first
Bulky / progressive pNET needing response	CAPTEM is particularly attractive; PRRT is also a strong option if homogeneously SSTR+
Progressive pNET without urgent shrinkage	PRRT / sunitinib / everolimus according to biology, prior therapy and access
SSTR-negative progressive GI NET	Everolimus or other systemic/local therapy according to site and behaviour
Previously treated progressive pNET or epNET	Cabozantinib is an evidence-based later-line option where available/reimbursed

Somatostatin analogues (SSA)

- Lanreotide 120 mg every 4 weeks or octreotide LAR 30 mg every 4 weeks provide hormonal control and antiproliferative activity. PROMID/CLARINET established tumour-growth control in appropriate well-differentiated NET.
- Dose/interval escalation can improve refractory hormonal symptoms; evidence for antiproliferative benefit beyond radiological progression is limited and should not delay an active tumour-directed therapy when progression is clinically relevant.

Pancreatic NET — key systemic options

Option	When particularly useful
CAPTEM	Need for objective response, bulky/faster-growing pNET, higher G2 and selected NET G3.
PRRT	Homogeneous SSTR+ progressive disease; increasingly considered early in higher G2.
Sunitinib	Evidence-based option in progressive pNET; generally modest response rate.
Everolimus	Evidence-based option in progressive pNET; useful when disease control rather than rapid shrinkage is the goal.
Cabozantinib	Active in previously treated progressive pNET; toxicity requires active management.

NEUROENDOCRINE NEOPLASMS

PRRT — MOVING EARLIER IN THE TREATMENT PATHWAY

Who is a candidate?

- Well-differentiated, unresectable/metastatic NET with sufficient and preferably homogeneous SSTR expression, appropriate renal/bone-marrow reserve and no dominant SSTR-negative aggressive disease.
- For higher G2/NET G3 or unexpectedly rapid progression, dual SSTR/FDG imaging helps identify discordant FDG+/SSTR– lesions that may make PRRT less appropriate.

Evolution of evidence

Trial	Population	Key message for practice
NETTER-1	Progressive SSTR+ midgut NET after SSA	Established 177Lu-DOTATATE after progression on SSA.
NETTER-2	First-line advanced G2/G3 GEP-NET; Ki-67 10–55%	Major PFS benefit vs high-dose octreotide; supports early/first-line PRRT in selected higher-proliferative SSTR+ disease.
COMPETE (2026)	Progressive SSTR+ G1/G2 GEP-NET; 85% treated in second line	177Lu-edotreotide superior to everolimus for PFS (23.9 vs 14.1 mo; HR 0.67), strengthening earlier PRRT sequencing.

PRRT has moved earlier in the treatment pathway

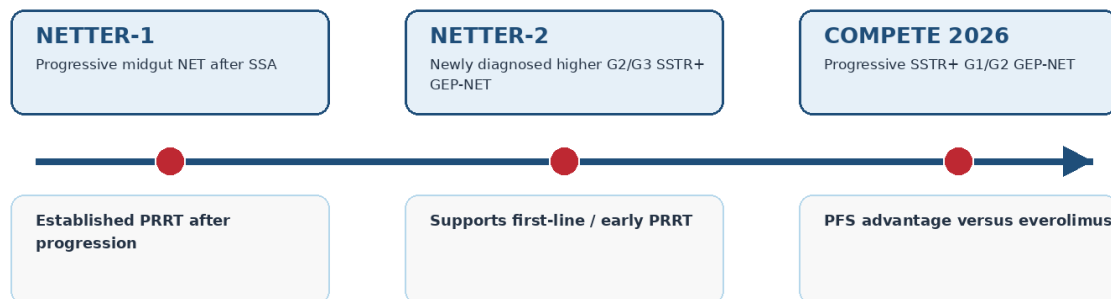


Figure 3. Evolution of randomized PRRT evidence from post-SSA therapy toward earlier treatment.

UZA 2026 INTERPRETATION

- NETTER-2 does not mean that every G2 NET should receive first-line PRRT. The decision should integrate Ki-67, pace, SSTR homogeneity, FDG phenotype, tumour burden, primary site and need for response.
- COMPETE provides randomized head-to-head evidence against everolimus in progressive SSTR+ G1/G2 GEP-NET and further shifts the sequencing discussion toward PRRT.

Practical PRRT points

- Standard 177Lu-DOTATATE treatment is typically delivered as four cycles with renal-protective amino-acid infusion; continue SSA for functional symptom control as clinically indicated.
- Acute nausea is commonly related to amino-acid infusion. Monitor cytopenias and renal function; late myeloid neoplasms are uncommon but relevant long-term risks.
- Re-treatment (re-PRRT) may be considered in selected patients with a meaningful prior durable response, but evidence is less robust than for initial PRRT and selection should be multidisciplinary.

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WELL-DIFFERENTIATED NET G3

CORE MESSAGE

- NET G3 is a well-differentiated neuroendocrine tumour with Ki-67 >20% and must not be managed automatically as poorly differentiated NEC.

Work-up

- Expert pathology review is recommended. Record morphology, Ki-67 hotspot and mitotic count; re-biopsy should be considered when clinical behaviour changes substantially.
- Perform SSTR-PET; strongly consider FDG-PET. Dual imaging is recommended before PRRT in NET G3 to avoid treating patients with major FDG+/SSTR- discordant disease.

Advanced NET G3 — practical selection

Situation	Preferred approach / options
Homogeneous SSTR+, Ki-67 20–55%, no major FDG/SSTR mismatch	PRRT is a first-line option; NETTER-2 supports substantial activity. It is not established as the universal first-line standard for every NET G3.
Pancreatic NET G3 / need for tumour shrinkage	CAPTEM is a strong option; FOLFOX is another active regimen.
SSTR-negative, Ki-67 <55%	Chemotherapy (e.g. CAPTEM or FOLFOX) generally preferred.
Ki-67 >55% / very aggressive behaviour	Evidence for PRRT is lacking; re-check diagnosis for NEC and favour chemotherapy according to biology.
After first-line chemotherapy	Consider PRRT if homogeneous SSTR+; otherwise alternative chemotherapy / trial.
After first-line PRRT	Chemotherapy is a logical next option; clinical trial whenever possible.

DO NOT DO

- Do not use platinum-etoposide as the default regimen for a well-differentiated NET G3, particularly when Ki-67 is <55%; activity is substantially lower than in true NEC.

Liver-dominant metastatic NET

- In selected patients consider resection, ablation, embolization/chemoembolization or radioembolization. Integrate liver-directed therapy with the systemic strategy in a NET MDT rather than treating it as a separate pathway.

Cabozantinib after prior therapy

CABINET cohort	Median PFS	Interpretation
Pancreatic NET	13.8 vs 4.4 mo (cabozantinib vs placebo)	Strong later-line activity; ORR ~19%.
Extra-pancreatic NET	8.4 vs 3.9 mo	Meaningful PFS benefit; lower response rate than in pNET.

- Cabozantinib is active but not a low-toxicity treatment; hypertension, fatigue, diarrhoea, hand-foot syndrome and dose reductions are clinically relevant.

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POORLY DIFFERENTIATED DIGESTIVE NEC

Diagnostic features

- Poorly differentiated small- or large-cell morphology, high proliferation (often Ki-67 >55%), aggressive clinical course; TP53/RB1 abnormalities are common. SSTR expression is often low or heterogeneous.

Localized disease

- Multimodal treatment is usually required because distant relapse risk is high. Depending on site and resectability: surgery plus platinum-based chemotherapy, or definitive chemoradiation when radical surgery would be highly morbid.

Metastatic disease — first line

Regimen	Position
Platinum + etoposide	Standard backbone; carboplatin can substitute for cisplatin according to fitness/comorbidity.
Cisplatin + irinotecan	Reasonable alternative. TOPIC-NEC did not demonstrate OS superiority over EP.

Molecular profiling

- Broad NGS is reasonable in advanced NEC. At minimum assess MMR/MSI; in colorectal/gastric primaries consider BRAF and HER2 where relevant, plus tumour-agnostic actionable alterations when comprehensive profiling is available.
- Single-agent immune checkpoint inhibition has limited activity in unselected NEC; use immunotherapy primarily for a validated predictive biomarker (e.g. MSI-H/dMMR) or in a clinical trial.

Second line

- No universally accepted standard. FOLFIRI and FOLFOX are commonly used options; temozolomide-based treatment may be considered in selected biology. Clinical trial is strongly preferred whenever available.

NET G3 vs NEC — one-line rule

- Well differentiated = NET pathway. Poorly differentiated = NEC pathway. Ki-67 informs biology and treatment intensity but does not replace morphology.

What's new? — 2024–2026

Update	Why it matters
NETTER-2	Moves PRRT into the first-line discussion for selected SSTR+ higher G2/G3 GEP-NET.
ENETS NET G3 position statement 2025	Formalizes NET G3 as a distinct treatment problem; supports PRRT or chemotherapy and dual PET selection.
CABINET	Establishes cabozantinib as an active option after prior therapy in pNET and extra-pancreatic NET.
COMPETE 2026	PRRT with ¹⁷⁷ Lu-edotreotide outperformed everolimus for PFS in progressive SSTR+ G1/G2 GEP-NET.

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UZA TREATMENT SUMMARY

Advanced GEP-NET / NEC — at-a-glance

Clinical scenario	Preferred direction
Stable/slow SSTR+ G1/low-G2 NET	SSA
Progressive SSTR+ GI NET	PRRT
Higher G2 (especially Ki-67 $\geq 10\%$), SSTR+	Consider early PRRT
Bulky/progressive pNET needing response	CAPTEM; PRRT also strong if homogeneous SSTR+
Progressive pNET, no urgent response need	PRRT / sunitinib / everolimus according to context
Previously treated progressive pNET/epNET	Cabozantinib among evidence-based options
SSTR-negative progressive GI NET	Everolimus / other systemic or local therapy
Well-differentiated NET G3	PRRT and/or CAPTEM/FOLFOX according to SSTR/FDG phenotype and need for response
Poorly differentiated NEC	Platinum-etoposide (or platinum-irinotecan)
MSI-H/dMMR NEN	Immunotherapy according to indication/access

SEQUENCING PRINCIPLE

- There is no universal sequence. Reassess biology at each major decision point: primary site, differentiation, Ki-67 as a continuous variable, SSTR expression, FDG avidity, disease tempo, tumour burden, functional status, previous treatment and need for objective response.

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