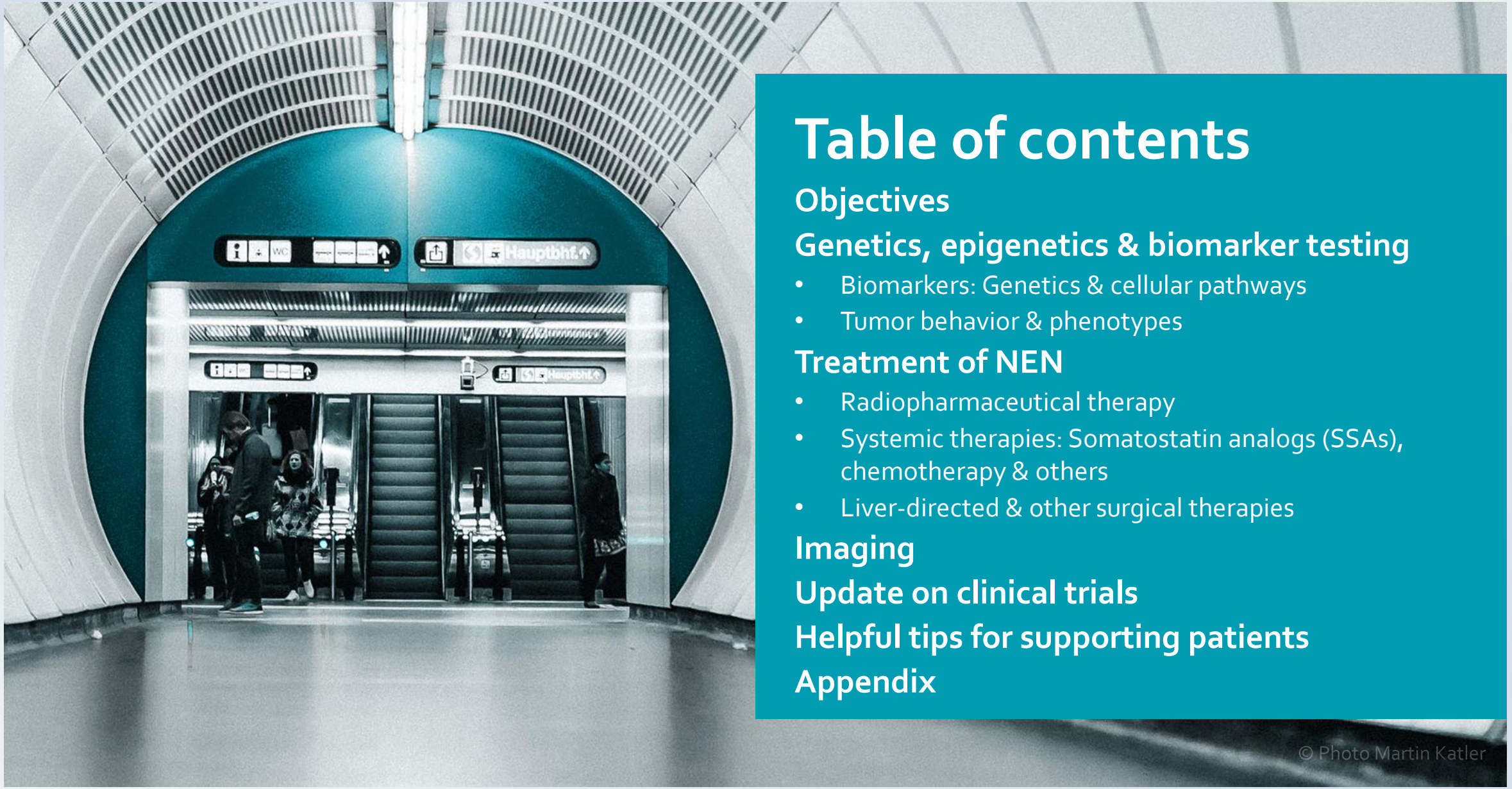
THERANOSTICS

21ST ANNUAL ENETS CONFERENCE

March 13 – 15, 2024
VIENNA, AUSTRIA

Disclaimer

The presentations and posters cited in this report were presented at the European Neuroendocrine Tumor Society (ENETS) conference held March 13th to 15th, 2024, in Vienna, Austria. This report contains a summary of the ENETS 2024 conference. Statements within this report may contain information about investigational or unapproved treatments. Use or reliance on the provided information is at your own risk.



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Objectives of this report

The 21st Annual ENETS (European Neuroendocrine Tumor Society) Conference was hosted at the Austria Center Vienna from March 13th to 15th. It drew over 1,100 participants, both physical and virtual, from various corners of the world.

The 3-day event was a testament to the multidisciplinary approach in NET management. It delved into a wide range of topics, including diagnosis, imaging, molecular testing, treatment, and follow-up, all of which were presented and discussed in a collaborative, MDT-based setting.

Objectives of this report are to:

- Inform healthcare professionals about the highlights from ENETS 2024
- Provide expert opinions on the clinical relevance of the new data for daily practice

This report primarily highlights the latest developments in clinical and basic/translational research related to neuroendocrine neoplasms. It includes updates on drug development, emerging imaging and surgical techniques, and recent advancements in radiopharmaceutical therapy. Additionally, a separate section is dedicated to patient-supporting tips, which are based on patient-driven research and insights shared at a nurse and dietician symposium held during ENETS 2024.

Genetics, epigenetics & biomarker testing

Biomarkers: Genetics & cellular pathways

NEN genetics and druggable targets

- NEN can carry a wide range of genetic alterations, which can be classified by the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT)
- A large series of NEN were profiled – potential drug-targetable genetic alterations were identified in 41% of tumors
  - Of these, 29% were treated with targeted antitumor therapy (TAT)
    - Of these, 67% experienced a clinical benefit
- Median overall survival in G3 NEN with ESCAT I-IV genetic alterations treated with TAT (n=12) was **45.7 months** compared to **17.2 months** in those treated with no TAT (n=31)
  HR: 0.46 [0.21-1.02]; p=0.051

Frequency of genetic alteration by ESCAT scale and grade

ESCAT	Tier I		Tier III		Tier IV	
Tumor Grade	Genetic alteration	N (%)	Genetic alteration	N (%)	Genetic alteration	N (%)
G1-G2	RET fusion TMB-H	1(2.1) 1(2.1)	ATM TSC2	1(2.1) 1(2.1)	PTEN ARID1A KRAS no-G12C CDKN2A	2(4.2) 2(4.2) 1(2.1) 2(4.2)
G3	MSI-H TMB-H BRAF V600E	3(4.1) 10(13.8) 3(4.1)	EGFR KRAS G12C PI3KCA IDH-1 BRCA ATM HRAS HER2 amp TSC2 FLT3	1(1.4) 1(1.4) 3(4.1) 1(1.4) 5(6.8) 4(4.1) 1(1.4) 2(2.7) 3(4.1) 1(1.4)	PTEN ARID1A KRAS no-G12C CDKN2A NOTCH CCND1	6(8.3) 5(6.9) 11(15) 3 4.1) 2(2.7) 2(2.7)

G, grade; **NEN,** neuroendocrine neoplasm; **HR,** hazard ratio; **TAT,** targeted antitumor therapy
Farinea G et al., ENETS 202:F04

Therapy-driven high-grade transformation in metastatic panNET

- Over time, NEN can progress from low grade G1 to high grade G2 or G3 tumors
- Backman et al. subjected paired metachronous tumor samples to WGS, RNA-seq and methylation array analysis or exome sequencing
- Some mutations are associated with anticancer therapy, especially alkylating agents
- High mutational burden can make tumors more aggressive and resistant to therapy
- Treatment-related hypermutation could have a potential role in immunotherapy

G, grade; **indel**, insertion/deletion; **NEN**, neuroendocrine neoplasms; **panNET**, pancreatic neuroendocrine tumor; **RNA**, ribonucleic acid; **WGS**, whole-genome sequencing.
Backman S et al., ENETS 2024:A03

A "molecular transition group" between low and high-grade neoplasms is identified via integrated molecular analysis of lung NEN with different Ki67 indices

- Simbolo et al. graded 126 lung NETs with carcinoid morphology using GEP-NET grading criteria and divided them into four groups according to the Ki67 index (G1, G2, G3, NEC)
- Unsupervised and supervised (deep learning) genomic analyses were performed, and mutational signatures of each group were identified
- Unsupervised analysis revealed three main clusters: NET, META-NE and NEC+, each with distinct signatures
- The G2 category showed two subgroups of which one was driven by NANOG and POU5F1 activity
  - G2 could be at the crossroads to G3 and NEC-like transition
- Unsupervised analysis highlighted a transitionary group supporting the hypothesis of molecular transition in Lung NEN

Distribution of tumor grades in the study population

Class	n (N=126)	Ki67%
G1	20	≤3
G2	52	4-20
G3	9	>20
NEC	45	>20

G, grade; **GEP**, gastroenteropancreatic; **NEC**, neuroendocrine cancer; **NEN**, neuroendocrine neoplasm; **NET**, neuroendocrine tumor.
Simbolo M et al., ENETS 2024:A22

Understanding the metabolic heterogeneity of panNET to predict response to treatment and identify new targets

Plasma-based metabolomic profiling of panNET[1]

- Plasma samples from 76 patients with panNET were compared to 38 people without cancer, accounting for age, sex and diabetic status
- Patients with panNET showed reduced one-carbon, creatine and branched-chain amino acid metabolism
- Similar to other NETs, metabolism in acyls, carnitine and complex lipids was reduced
- Specific metabolic plasmatic signatures were defined for different tumor characteristics (*MEN1* mutation, metastasis)

MCT1 and MCT4 in the crosshair for precision therapy[2]

- MCT4 and MCT1 monocarboxylate transporters and CA9 expression in panNET by IHC analysis were investigated
- MCT1/4/CA9 expression patterns that defined three metabolic subtypes with different patient outcomes were identified
- MCT1 and MCT4 were shown to direct lactate efflux in panNET cells cooperatively
- MCT1/4 inhibition reduced metabolic activity, growth and metabolic heterogeneity of patient-derived panNET tumoroids
- Combination with angiogenesis inhibitors might potentiate efficacy

IHC, immunohistochemistry; **NET,** neuroendocrine tumor; **panNET,** pancreatic neuroendocrine tumor.

1. Jannin A et al., ENETS 2024:F07. 2. Bräutigam K et al. ENETS 2024: B01.

Experts' comments

- Neuroendocrine neoplasms (NEN) can exhibit a wide range of genetic and molecular alterations.
  - Identifying these alterations may help in grouping them together and potentially identifying future drug targets.
- NEN can transition from low-grade to high-grade tumors over time, sometimes due to treatments received, e.g., pancreatic NETs being treated with alkylating agents.
  - Deep learning genomic analyses could help us to identify mutational signatures for these tumors, potentially increasing our understanding of their heterogeneity and identifying new therapeutic avenues.
- An improved understanding of metabolic heterogeneity in patients with pancreatic NET could help in identifying a metabolomic signature to predict their response to treatment.
- A molecular transition group, as presented by Simbolo et al., needs to be considered in the context of extrapulmonary NEN, as their evolution may differ.
  - A similar distinction between GI and extra-GI origins needs to be considered regarding genetics and druggable targets.

NEN, neuroendocrine neoplasm; NET, neuroendocrine tumor

Tumor behavior & phenotypes

Size of nodal metastases in patients with NF-panNET may be a predictor of disease relapse/recurrence

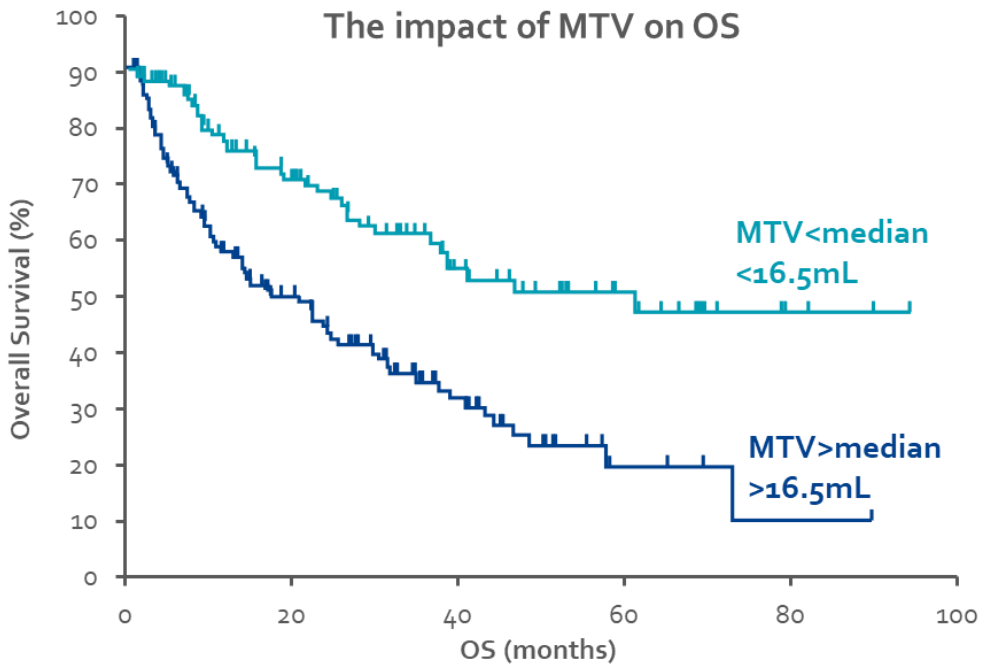
- Nodal metastases are a powerful predictor of relapse in patients with NF-panNET after surgery with curative intent
  - However, not all patients with nodal metastases relapse – Andreasi et al. asked, whether the *size* of nodal metastases is a useful predictor of relapse
  - Nodal metastases were classified as:
    - Micrometastases (<5 mm), or
    - Macrometastases (≥5 mm)
- 100 patients submitted to panNET resection were analyzed:
  - 42 had nodal metastases (N+)
  - 58 had no nodal involvement (No)

- Micro- vs. Macrometastases
  - Tumor grade (G2-G3) and Ki67 proliferative index were significantly higher in patients with Macrometastases vs. Micrometastases (p=0.009 and p=0.006, respectively)
- Disease recurrence & disease-free survival (DFS)
  - Micrometastases (vs. No) was not significantly associated with disease recurrence (p=0.081)
  - Macrometastases (vs. No) was an independent determinate of disease recurrence **HR: 6.281 [95% CI: 1.238-27.419]; p=0.034**
  - Similarly, DFS was significantly lower for patients with Macrometastases vs. No (p=0.046), but not significantly different for Micrometastases vs. No (p=0.152)

CI, confidence interval; **DFS,** disease-free survival; **G,** grade; **HR,** hazard ratio; **M,** metastasis; **N,** node; **NF,** non-functioning; **panNET,** pancreatic neuroendocrine tumor.
Andreasi V et al., ENETS2024:E03

Could metabolic tumor volume (MTV) be a biomarker for patients with GEP-NEN?

- FDG avidity in NEN predicts higher histological grade and poor prognosis, but there is insufficient evidence for FDG-avid tumor volume as a marker
- Chan et al. performed a retrospective study, involving 231 patients at a median follow-up of 27 months
- The median MTV was 16.5 mL; patients with an MTV>16.5 mL had a poorer prognosis vs. patients with an MTV<16.5 mL
- mOS = 23.8 vs. NR
  HR:2.49 [1.69-3.66];p<0.0001
- Patients with high volumes of FDG avid disease might qualify for more aggressive therapy



Median OS: 23.8 mo vs. NR,
HR 2.49 (1.69-3.66), p<0.0001

FDG, Fluorodeoxyglucose; **GEP-NEN**, gastroenteropancreatic neuroendocrine neoplasm; **HR**, hazard ratio; **mo**, months; **mOS**, median overall survival, **MTV**, metabolic tumor volume; **NR**, not reached.
Chan D et al., ENETS2024:H05

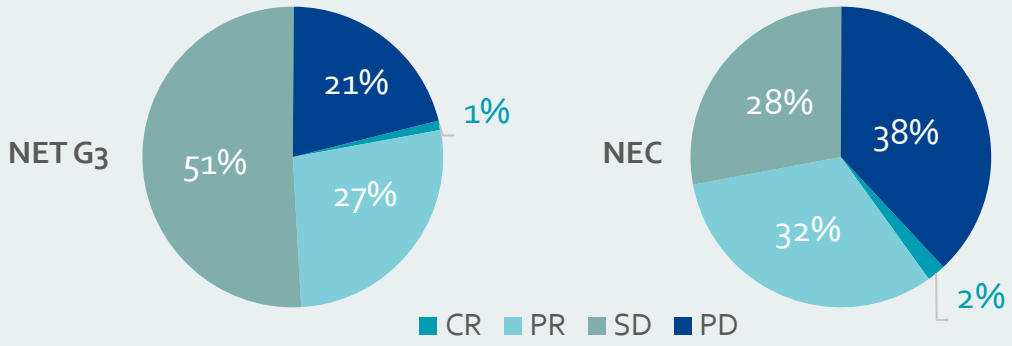
Nordic NEC 2: Characteristics and treatment outcomes in a patients with high-grade (G3 and NEC) digestive NEN

- Nordic NEC 2 was a prospective study involving 698 cases of high-grade digestive NEN (NET G3 n =128; NEC n = 511)
- Patients received one of three chemotherapy regimes (see table)
- Results
  - Prognostic factors for OS
    - NEC: Age, sex, PS 1, PS 2, Ki-67 55%, ALP
    - NET G3: Age, PS, ALP
  - Ki-67 (threshold 55%) was a predictive factor in NET G3 and NEC
    - NET G3 patients with Ki-67<55%: Platin/Epo (mOS = 14.3 m) was inferior to treatment with TEMCAP (22.5 m) or TEM/EVE (31.4 m); no significant differences in NEC
    - NET G3 with Ki-67>55% had a similar initial survival as NEC

First-line treatment

	NET G3	NEC
n	116	426
Carbo/cisplatin + etoposide	45	353
TEMCAP	28	19
Temozolomide/Everolimus*	28	8
mOS after first-line chemotherapy, months	21.8 (17.2-26.3)	7.4 m (6.3-8.4)
mPFS after first-line chemotherapy, months	9.9 (8.0-11.7)	6.1 (5.5-6.7)

Best response by tumor grade



ALP, alkaline phosphatase; **CAP**, capecitabine; **CR**, complete response; **Epo**, etoposide; **EVE**, everolimus; **G**, grade; **NEC**, neuroendocrine cancer; **NEN**, neuroendocrine neoplasia; **NET**, neuroendocrine tumor; **OS**, overall survival; **PD**, progressive disease; **PFS**, progression-free survival; **PR**, partial response; **PS**, performance score; **SD**, stable disease; **TEM**, temozolomide

Sorbye H et al., ENETS2024:I24

Evaluating current and upcoming criteria for the histopathological classification of lung NETs

The strengths and limitations of current WHO classifications and prognostic markers were evaluated using data from the lungNENomics project via the Pathonet deep learning model[1] and unsupervised Barlow twins deep learning model[2,3] to identify new morphological features

Results

Classification into typical and atypical carcinoids (TC/AC) is prone to misdiagnosis

Ki-67 improves high-risk TC detection but not AC specificity; PHH3 speeds up mitotic counting; automatic evaluation reaches the performance of experts

Barlow-Twins outperforms in classifying tumors by molecular profiles[4] compared to their histological types, opening new perspectives for more molecular classification

AC, atypical carcinoid; **LNET**, lung neuroendocrine tumor; **NEN**, neuroendocrine neoplasm; **PHH3**, phosphorylated histone H3; **TC**, typical carcinoid.

Matian E et al., ENETS2024:A17:4134. 1 Negahbani F et al., Sci Rep. 2021 Apr 19;11(1):8489. 2 Zbontar J et al., arXiv: 2103.03230. 3 Quiros A et al, arXiv :2205.01931v3. 4 Alcala N et al., Nat Commun 10, 3407 (2019).

Experts' comments

- Studies with large cohorts not only help to identify suitable therapies but also to avoid unnecessary ones, as in the case of platin/etoposide for patients with NET G3.
- Currently, the most used prognostic factors for NEN include morphological differentiation categories, which classify the tumors as NETs or NECs, the Ki-67 index, and the mitotic count.
- Investigating new prognostic markers provides valuable information about the progression of disease in NEN. These markers, such as the size of nodal metastases in panNET or the metabolic tumor volume in GEP-NETs, may reveal important mechanistic details regarding the risk for metastasis and recurrence or overall survival.

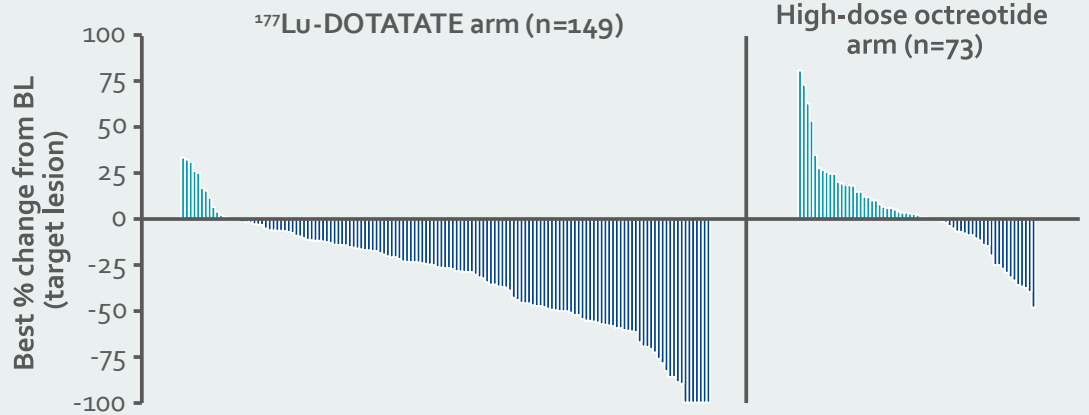
NEC, neuroendocrine cancer; **GEP-NET**, gastroenteropancreatic neuroendocrine tumor, **NET**, neuroendocrine tumor; **panNET**, pancreatic neuroendocrine tumor

Treatment of NEN

Radiopharmaceutical therapy

Practice-changing data for RPT in G2/G3 GEP-NETs

- NETTER-2, the first phase 3 trial to assess RPT as first-line treatment, showed ^{177}Lu-DOTATATE reduced the risk of progression or death by 72% compared with high-dose octreotide in higher grade, well-differentiated GEP-NETs
- RPT significantly prolonged median PFS by 14.3 months and was consistent as per central and local assessments
- ORR was significantly higher for RPT, with almost 83% of the patients receiving RPT had some degree of tumor shrinkage
- No new safety issues were reported, and both treatment arms showed similar QoL profiles
- Ongoing phase 3 trials, COMPETE† and COMPOSE‡, aim to provide more information on the optimal treatment sequence in advanced well-differentiated GEP-NETs



	^{177}Lu-DOTATATE arm (n=149)	High-dose octreotide (n=73)
Decrease in best % change from BL	**82.6%**	**34.2%**
Increase / no change in best % change from BL	10.7%	50.7%
% change not available	5.4%	12.3%
% change contradicted by overall lesion response = PD	1.3%	2.7%

Only patients with measurable disease at baseline included

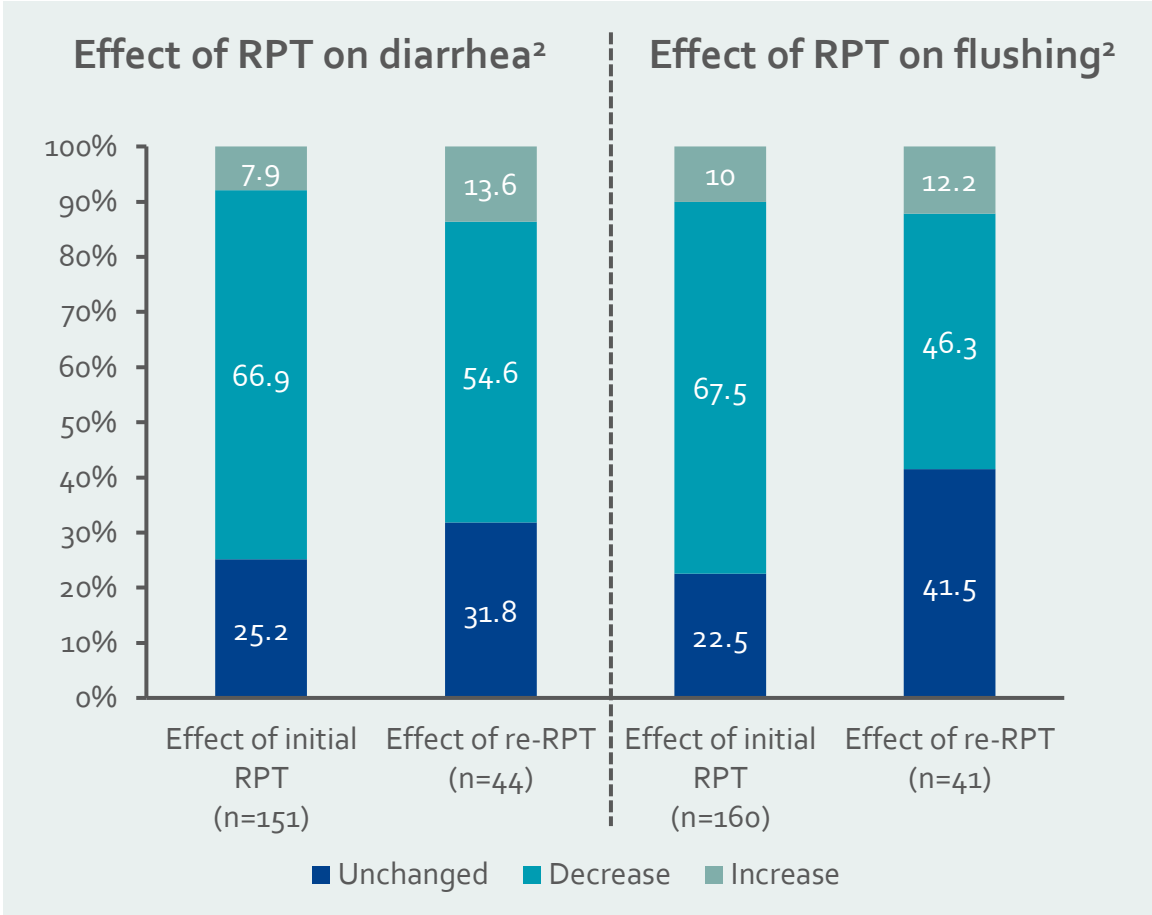
177Lu, lutetium-177; **BL**, baseline; **G**, grade; **GEP-NET**, gastroenteropancreatic neuroendocrine tumor; **ORR**, objective response rate; **PD**, progressive disease; **PFS**, progression-free survival; **QoL**, quality of life; **RPT**, radiopharmaceutical therapy.

De Herder W. ENETS 2024;5A:H06.

†NCT03049189 ‡NCT04919226

RPT effectively controls symptoms in functional NEN

- RPT is recommended in unresectable and metastatic GEP-NETs; however, recommendations for functional NEN (F-NEN) are not well-established
- In a retrospective study of 45 cases of RPT treatment in F-NEN, 43 cases showed clinical benefit (95.6%), with improvement or resolution in diarrhea, flushing, abdominal pain and hypoglycemia[1]
- A single-center retrospective cohort analysis showed a decrease in symptoms of flushing and diarrhea in two thirds of patients with CS after initial RPT and in nearly half of patients after salvage RPT[2]
- The symptomatic control was associated with an u5-HIAA reduction of ≥30% in 48.3% after initial RPT and in 17.7% after salvage RPT[2]
- A smaller cohort was analyzed for tryptophan metabolism, which showed a significant decrease of serotonin after two and four cycles of RPT and a significant reduction in 5-HIAA only after four cycles of RPT[2]



5-HIAA, 5-hydroxyindoleacetic acid; **CS,** carcinoid syndrome; **GEP-NET,** gastroenteropancreatic neuroendocrine tumor; **NEN,** neuroendocrine neoplasm; **RPT,** radiopharmaceutical therapy.

1. Lopes-Pinto M. ENETS 2024:H09. 2. Maas CF. ENETS 2024:H10

RPT re-treatment favorable in lung and GEP-NETs

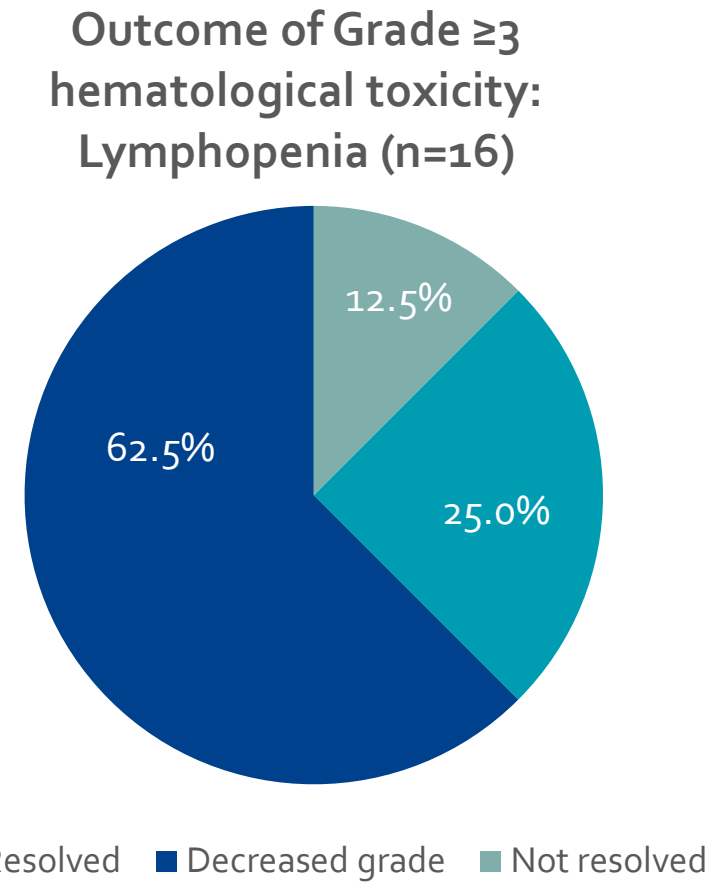
- Despite progress with RPT for GEP-NETs, key issues remain with RPT as a re-treatment option for patients with advanced GEP-NET or lung NET
- Re-treatment with lutetium-based RPT following standard-dose RPT demonstrated an ORR of 4.5% and a DCR of 59.1% (see table)[1]
- PFS upon re-treatment was 11.5 months, and OS of 27.7 months (see table)[1]
- The IRST Dino Amadori experience showed a 5-year OS of 91.7 % and a median PFS of 18.6 months with salvage RPT[2]
- Patients who had PFS greater than 3 years following initial RPT had a statistically significant difference in median PFS after RPT re-treatment compared to patients with PFS less than 3 years, indicating the need for appropriate patient selection prior to RPT

	Initial RPT	Re-RPT
No. of cycles	4	3(1-4)
ORR (%)	17 (54.8%)	1* (4.5%)
DCR (%)	31 (100%)	13* (59%)
mPFS (months)	29.37 months (95% CI, 13.8-120.67)	11.5 months (95% CI, 9-14)
OS (months)	–	27.7 months (95% CI, 14.7-40.6)
AEs G3-4	12.9% lymphopenia 3.2% leukopenia 3.2% nephrotoxicity	12.9% thrombocytopenia 9.7% lymphopenia 6.5% anemia 3.2% leukopenia 0% nephrotoxicity

*22 patients were evaluable for response RR-RPT.
AE, adverse event; **CI,** confidence interval; **DCR,** disease control rate; **GEP-NET,** gastroenteropancreatic neuroendocrine tumor; **IRST,** cancer research institute of Romagna; **NET,** neuroendocrine tumor; **ORR,** objective response rate; **OS,** overall survival; **RPT,** radiopharmaceutical therapy.
1.Martinez-Lago N . ENETS 2024:H11. 2. Sansovini M. ENETS 2024:H19

Predicting and managing RPT-led hematological toxicity

- Radiation-induced damage to hematopoietic tissue is a major concern of RPT. Up to 10% of patients experience acute, grade 3 or 4, hematological toxicity, with a long-term risk of developing MDS
- Lymphopenia grade ≥3 was common (43%) during RPT in 37 GEP-NETs (observed prospectively), but the toxicity was transient and did not impact the RPT course[1]
- In a retrospective study, 17% of patients had PT two months post-RPT. Predictive factors for PT were an OMIS ≥30%, pelvic BM, and spleen length ≥100mm. The drop in platelet count after first RPT cycle should be closely monitored[2]



BM, bone metastases; **GEP-NET,** gastroenteropancreatic neuroendocrine tumor; **MDS,** myelodysplastic syndrome; **OMIS,** osteo-medullary invasion score; **PT,** persistent thrombocytopenia; **RPT,** radiopharmaceutical therapy.
1. Mileva M. ENETS 2024:H12. 2. Oziel-Taieb S. ENETS 2024:H16

RPT benefited patients with GEP-NETs who progressed after surgery

- The survival benefits of RPT following progression after surgical resection are unknown
- 237 patients with GEP-NETs who progressed after surgery received RPT (n=95) or other treatments (n=142)
- The RPT was associated with a longer median PFS and OS compared to the no-RPT
- In a subgroup analysis, RPT (upfront or delayed) was associated with an improved PFS for both small bowel NETs and panNET compared to no RPT
- Multivariable analysis showed RPT was independently associated with improved OS (HR:0.61 [0.39-0.95]; p=0.028)

First progression after surgical resection in patients with GEP-NETs

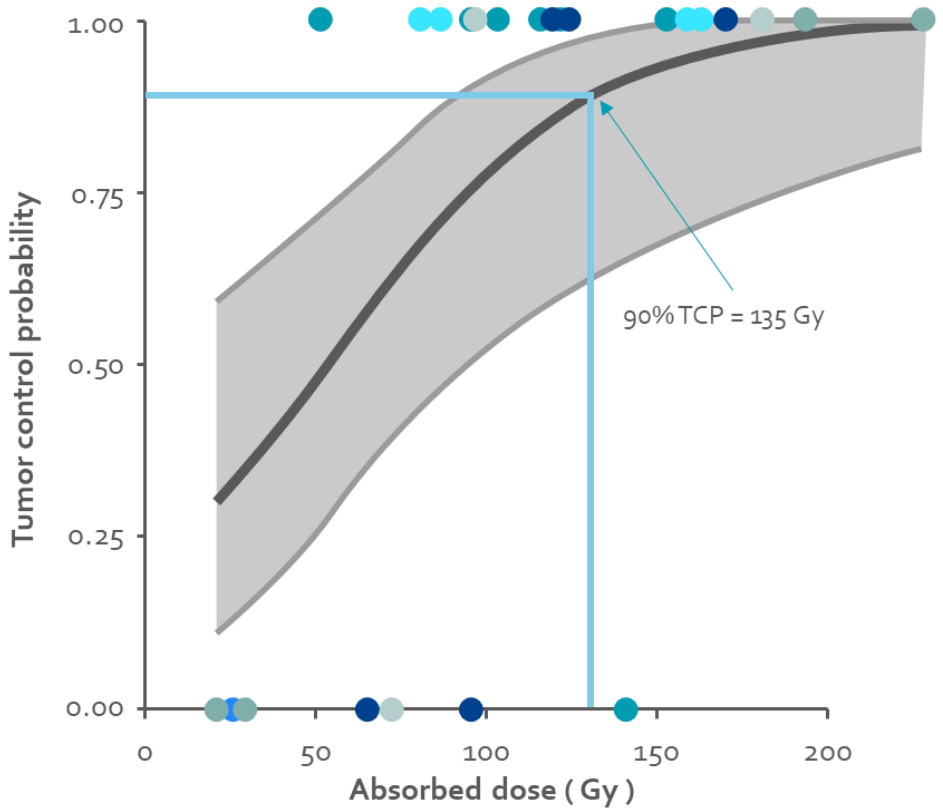
Attribute	No RPT (n=142)	RPT (n=95)	p
mPFS; months	32.4	11.0	<0.0001
mOS; months	49.8	38.4	0.009

GEP-NET, gastroenteropancreatic neuroendocrine tumor; **HR**, hazard ratio; **mOS**, median overall survival; **mPFS**, median progress-free survival; **NET**, neuroendocrine tumor; **OS**, overall survival; **PFS**, progression-free survival; **panNET**, pancreatic neuroendocrine tumor; **RPT**, radiopharmaceutical therapy.

Borbon LC. ENETS 2024:J06

When taken into consideration, dosimetry can influence individual RPT doses

Probability of tumor control (TCP) for G2 NETs, as a function of the cumulative absorbed dose over all cycles[1]



- RPT allows quantification of the absorbed dose of the drug in the body and potentially allows for individualized treatment of patients
- A clear relationship between absorbed dose and volume reduction in G2 NETs treated with dosimetry-guided Lu-RPT was shown in a retrospective study, suggesting a 90% probability of partial tumor response for an accumulated tumor absorbed dose of at least 135 Gy[1]
  - However, no such relationship could be identified for G1 NETs
- The DuoNen phase III study compared the safety and effectiveness of fixed-dose vs. individual dosimetry-based algorithms of two RPTs (Y-90 & Lu-177 based) for G1 and G2 NETs[2]
  - In 30 cycles with dose adjustment, the dose increased in 21 cases and decreased in 9 cases
  - Therefore, personalized renal and bone marrow dosimetry affected the individual RPT doses in each subsequent treatment cycle

G, grade; **Lu-177**, lutetium-177; **NET**, neuroendocrine tumor; **TCP**, tumor control probability; **RPT**, radiopharmaceutical therapy; **Y-90**, yttrium-90.

1. Warfvinge CF. ENETS 2024:H24. 2. Opalinska M. ENETS 2024:M07

RPT response differs based on metastases location

RPT response patterns may differ between hepatic/liver-only (LO) and extra-hepatic (LE) metastases.

A retrospective study compared the tumor growth rate (TGR) in GEP-NETs before and after RPT. The study found that patients with metastases in the LO had better responses to RPT.

Response using RECIST1.1	CR	PR	SD	PD	NE
All patients	1.4%	15%	76%	7.5%	2.9%
LO patients	6.6%	26.6%	60%	6.6%	0%
LE patients	0%	14.6%	80.4%	7.3%	0%

In patients with LO metastases who were treated with RPT, a non-significant trend towards better response and greater reduction in TGR was observed.

	TGR pre-RPT	TGR post-RPT	P-value
All patients	6.5%	-0.7%	0.00004
LO patients	4.53%	-2.18%	0.00003
LE patients	7.02%	-0.48%	0.0012

CR, complete response; **GEP-NET**, gastroenteropancreatic neuroendocrine tumor; **NE**, not evaluated; **PD**, progressive disease; **PR**, partial response; **RECIST**, Response Evaluation Criteria in Solid Tumors; **RPT**, radiopharmaceutical therapy; **SD**, stable disease; **TGR**, tumor growth rate.

1. Sánchez Gómez L. ENETS 2024:H18

Experts' comments

- The NETTER-2 study revealed practice-changing data, demonstrating that ^{177}Lu-DOTA-TATE + SSA, which was previously approved for the treatment of low-grade GEP-NETs, is also effective without any new safety concerns in higher-grade GEP-NETs.
  - The upcoming subgroup analysis data from NETTER-2 will unveil a more precise patient population that may benefit the most from RPT as a first-line treatment.
- The ongoing phase 3 trials, COMPETE and COMPOSE, will address data gaps and provide information on the optimal treatment sequence for advanced well-differentiated GEP-NETs.
- Acute and long-term renal and hematological toxicity, including the risk of secondary malignancies, is a significant concern with RPT.
  - More extended follow-up data in RPT-treated patients is needed to address this concern.
- There is a current need for prospective trials testing personalized dosimetry-based RPT, which may improve outcomes by aiding treatment planning and establishing safe limits for healthy organs while providing sufficient doses to the tumor.

(GEP-)NET, (gastroenteropancreatic) neuroendocrine tumor; RPT, radiopharmaceutical therapy; SSA, somatostatin analog

Systemic therapies: Somatostatin analogs (SSAs), chemotherapy & others

Presence of malnutrition and its association with OS in SSA-treated patients with GEP-NETs

118 patients with GEP-NETs using SSAs treated at King's College Hospital in London were included in a cross-sectional study:

75% of patients (n=88) met the GLIM criteria for malnutrition (i.e., weight loss, low body mass index, and sarcopenia)

Meeting 2 or 3 GLIM criteria was significantly associated with worse overall survival (HR 2.16 [95% CI: 1.34-3.48]; *p*=0.002)

Out of the 3 GLIM criteria, weight loss was the most important risk factor (HR 3.5 [95% CI: 1.14-10.85]; *p*=0.03)

Patients could benefit from regular weight monitoring
and future research should focus on the effect of early nutritional interventions on overall survival.

CI, confidence interval; **GEP-NET,** gastroenteropancreatic neuroendocrine tumor; **GLIM,** Global Leadership Into Malnutrition; **HR,** hazard ratio; **OS,** overall survival; **SSA,** somatostatin analog.
1. Clement D et al. ENETS 2024; D17.

TEM is associated with grade progression and hypermutation in panNET

- Temozolomide (TEM), an alkylating agent, is a standard therapy for panNET
- In glioblastomas, TEM induces a hypermutator phenotype in a subset of patients through MMR deficiency
- In advanced colon cancer, TEM priming increases TMB, favoring immunotherapy efficacy

Grade progression and TMB in a monocentric cohort

- A cohort of low-grade TEM-treated panNET was analyzed pre- and post-treatment
- Grade increased from G1/G2 to G3 after TEM in 43% of TEM-treated panNET
- Matched samples (pre- and post-TEM) were sequenced by NGS using tissue or liquid biopsy, and a trend to higher TMB among 'increased' vs. 'stable' Ki-67 was observed
- TEM can increase both sub-clonal and clonal mutational burden → TMB-high post-TEM samples had alterations in the MMR genes, which may be immunogenic

Independent validation cohort

- 1079 panNET molecularly profiled:

25/1079 panNET were TMB-high

↓

- 67% had an alkylating-related DNA signature
- 44% had several MMR gene alterations

16/898 displayed a high alkylating-related signature

↓

88% were TMB-high

- These results suggest a key role of the treatment in the TMB status

DDR, DNA damage repair; **DNA,** deoxyribonucleic acid; **G,** grade; **MMR,** mismatch repair; **NGS,** next-generation sequencing; **panNET,** pancreatic neuroendocrine tumor; **TEM,** temozolomide; **TMB,** tumor mutation burden.

1. Trevisani E. ENETS 2024:A26. 2. de Mestier L. ENETS 2024:109

Combination therapies with TKI for heavily treated NETs

- Management of NEN is limited due to the eventual development of resistance to currently approved treatment options. Hence, combining different therapies to inhibit multiple pathways might have a synergistic effect
- New generation TKIs that have a wide range of activity are currently being actively researched

Combination with mTOR inhibitor[1]

- In a single-institute, phase II trial, patients with advanced, progressive ep-NETs were treated with Lenvatinib & Everolimus
- ORR: 40.7% with a benefit across all primary sites
- Reduced-dose Lenvatinib (14 mg PO daily) appeared to be well-tolerated

Combination with ICI[2]

- A single-arm basket study of Cabozantinib + Atezolizumab in four NEN cohorts: lungNET, malignant PPGL, GEP-NET and G3 EP-NEN
- Responses were observed in PPGL and GEP-NET, but not in LungNET and G3 EP-NEN, regardless of the dose intensity of Cabozantinib

Combination with chemotherapy

- Surufatinib + CAPTEM showed encouraging antitumor activity in patients with advanced G2 NETs[3]
  - ORR: 16.7%; DCR: 95.8%
- Real-world study of Surufatinib + HAIC in heavily pre-treated, high-grade NEN[4]
  - ORR: 44.4%; DCR: 100%

CAPTEM, capecitabine and temozolomide; **DCR,** disease control rate; **ep,** extrapancreatic; **G,** grade; **GEP,** gastroenteropancreatic; **HAIC,** hepatic artery infusion chemotherapy; **ICI,** immune checkpoint inhibitor; **mTOR,** mammalian target of rapamycin; **NEN,** neuroendocrine neoplasm; **NET,** neuroendocrine tumor; **ORR,** objective response rate; **PO,** oral administration; **PPGL,** pheochromocytoma/paraganglioma; **TKI,** tyrosine kinase inhibitor.

1. Dasari A. ENETS 2024:I08. 2. Molina-Cerrillo J. ENETS 2024:I21. 3. Wang W. ENETS 2024:I31. 4. Wang Y. ENETS 2024:I32

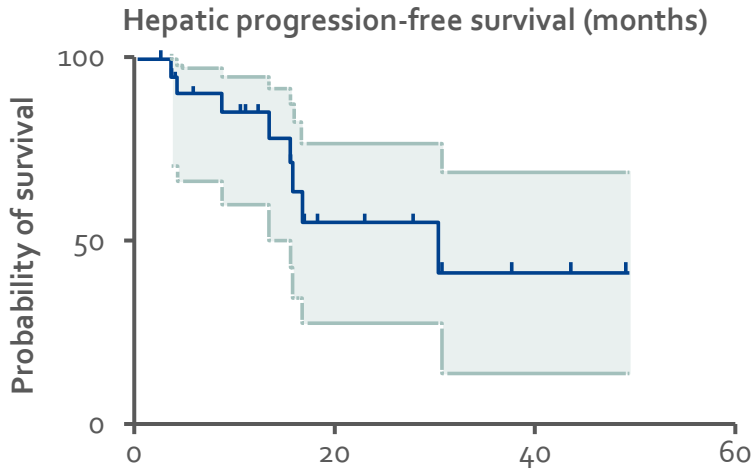
Experts' comments

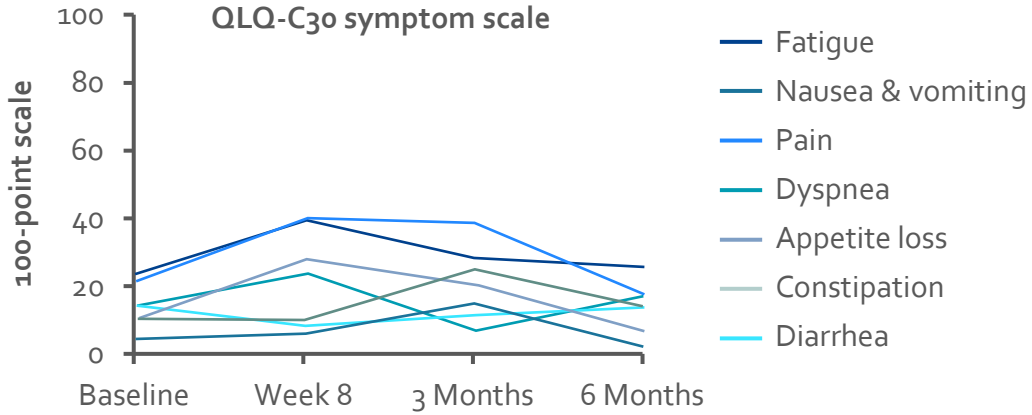
- Systemic therapy remains the mainstay treatment for unresectable and metastatic NEN, but complete responses are rarely achieved. Management of NEN is currently limited by the eventual development of resistance to approved therapies.
- Combination therapies inhibiting multiple pathways might be the future preferred choice, making use of synergistic effects. These include combining RPT with radiosensitizing agents such as PARP inhibitors or new-generation TKIs with other targeted agents that are currently being tested.
- The hypermutator effect of alkylating agents such as temozolomide presents interesting data that supports the potential future efficacy of immunotherapy. However, this initial data needs to be confirmed in larger prospective trials.

NEN, neuroendocrine neoplasm; PARP, Poly [ADP-ribose] polymerase; TKI, tyrosine kinase inhibitor

Liver-directed & other surgical therapies

Clinical efficacy and safety of TheraSphere SIRT for liver metastases in NETs





In a prospective study of 21 heavily pre-treated patients, SIRT demonstrated:

- Clinical efficacy, with a favorable ORR and a median liver-specific PFS greater than 2 years
- The safety profile was acceptable, with a low incidence and severity of treatment-related adverse events. At 6 months post-SIRT, there were no high-grade clinical or laboratory toxicities
- No significant deterioration in QoL outcomes at 6 months post-SIRT

→ **SIRT may be an effective strategy for the management of heavily pre-treated NETs with liver metastases.** Larger studies are needed to look at the effect of treatment sequences and multimodal therapy

NET, neuroendocrine tumor; **ORR,** objective response rate; **PFS,** progression-free survival; **QoL,** quality of life; **SIRT,** selective internal radiation therapy.

1. Ahmed Q et al. ENETS 2024; G01.

Liver transplantation for patients with NEN and unresectable liver metastases

Background

- Liver transplantation can be an option for patients with NEN
  - Multiple studies have showed median 10-year OS[1,2,3] and DFS > 10 years[1,3]
- Guidelines generally recommend transplantation only for select patients with unresectable, stable, liver-only G1/G2 disease
- A pilot study in Ireland and the UK: 4 patients selected by ENETS-CoE, were listed for liver transplantation and successfully transplanted
- Patients reported improved physical and psychological status

Case study

- A female patient, 60 years old, was initially diagnosed with NEN-related liver metastases in 2021
- Primary tumor was midgut G1 NET, Ki-67 <2%
- Stable liver-only disease; prognosis was 7-10 years life expectancy
- Was approved for liver transplantation in April 2023 and received transplant 7 months later
- Successful transplantation, unremarkable CT and ultrasound monitoring; currently (March 2024) 4 months post-op and awaiting post-transplant imaging

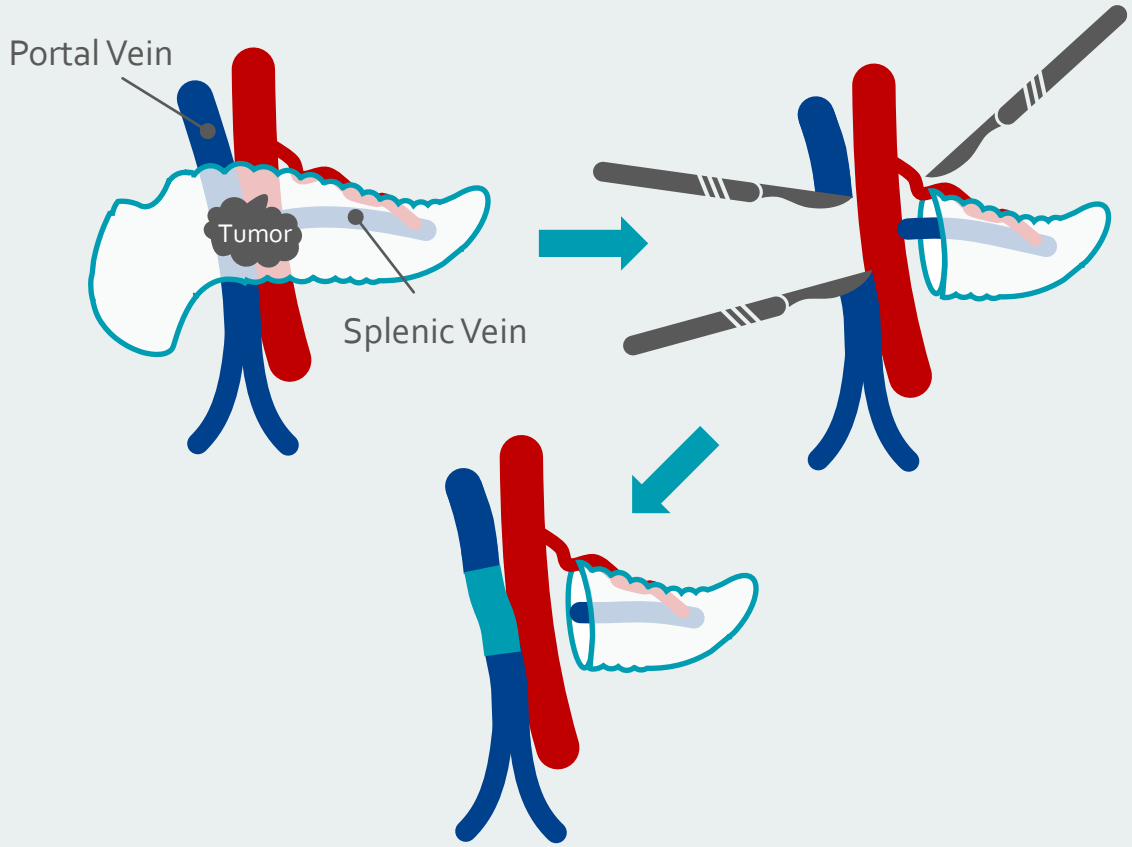
CT, computed tomography; **DFS,** disease-free survival; **ENETS-CoE,** European Neuroendocrine Tumor Society Cluster of Excellence; **G,** grade; **NEN,** neuroendocrine neoplasm; **OS,** overall survival.

Smith S, ENETS2024; Jarvis N, ENETS2024. 1. Mazzaferro V et al., Am J Transplant 2016 Oct;16(10):2892-2902. 2. Valvi D et al., K Gastrointest Surg. 2021 Jun;25(6):1487-1493. 3. Maspero M et al. Am J Transplant. 2022 Nov; 22(11): 2598–2607.

Outcome and prognostic factors of portal vein resection in panNEN surgery

Portal vein resection could be considered in patients with advanced panNEN, as it can offer **excellent disease-specific as well as overall survival** if radical resection can be achieved

- Radical resection was associated with 5-year overall survival of 51% and 5-year disease-specific survival of 75%
- Complication rates after portal vein resection were comparable to standard resection:
  - With low perioperative morbidity and mortality, and
  - No significant differences in pancreas-specific post-operative complications



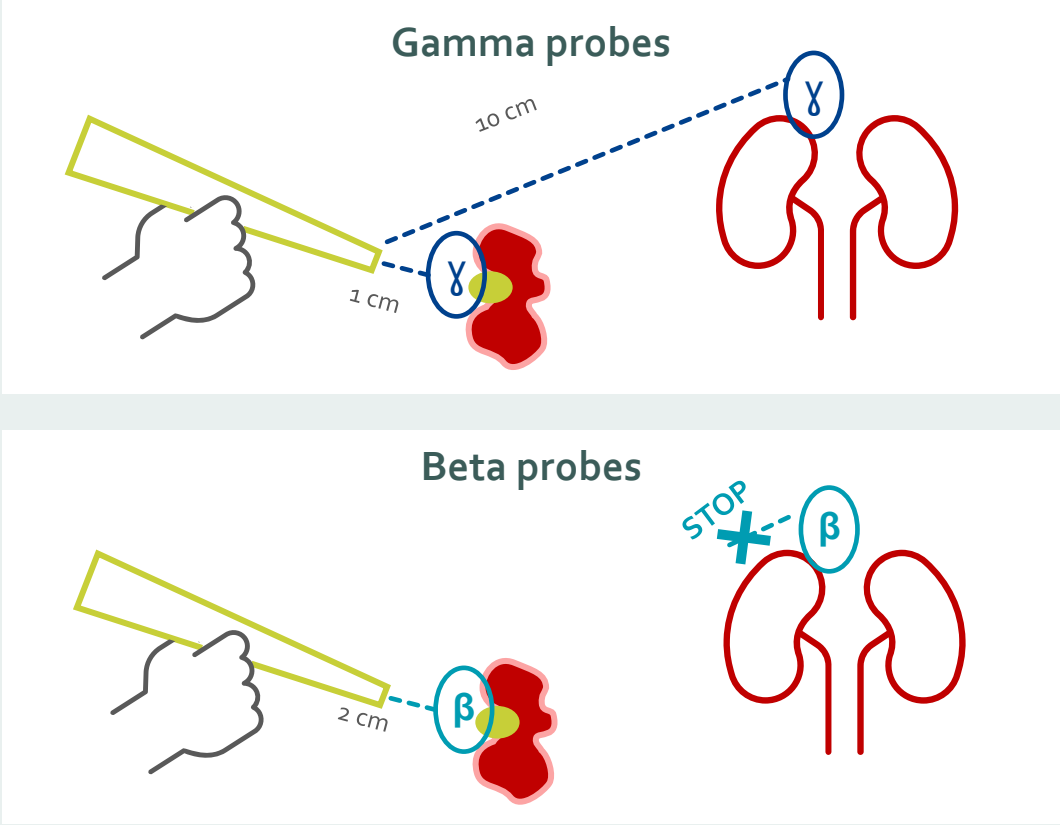
panNEN, pancreatic neuroendocrine neoplasm.

1. Nießen A et al. ENETS 2024; J13. 2. Nießen A et al. Surgery. 2024; 175(4): 1154-1161.

β-probe diagnostic accuracy for detection of small intestinal NET[1]

- The accuracy of ɣ-probes is limited, as they can pick up radiation emitted from distant organs with physiological uptake of radiopharmaceuticals.[2]
- Radio-guided surgery with a new generation β-probe for radiolabeled SSA was feasible and safe and **showed remarkable accuracy** (AUC=0.928).
  - With a TBR cutoff of 1.35, the sensitivity and specificity were 89.3% and 86.4%, respectively.
  - 13% of the specimens analyzed at pathology were identified as malignant only thanks to the use of the β-probe.
- Duration of surgery remained consistent.
- The mean absorbed dose by surgery staff was insignificant (30 µSv).

Radio-guided surgery has the potential to improve radical resection rates in SI-NETs, but larger studies are needed to evaluate the impact of this technique on clinical outcomes.

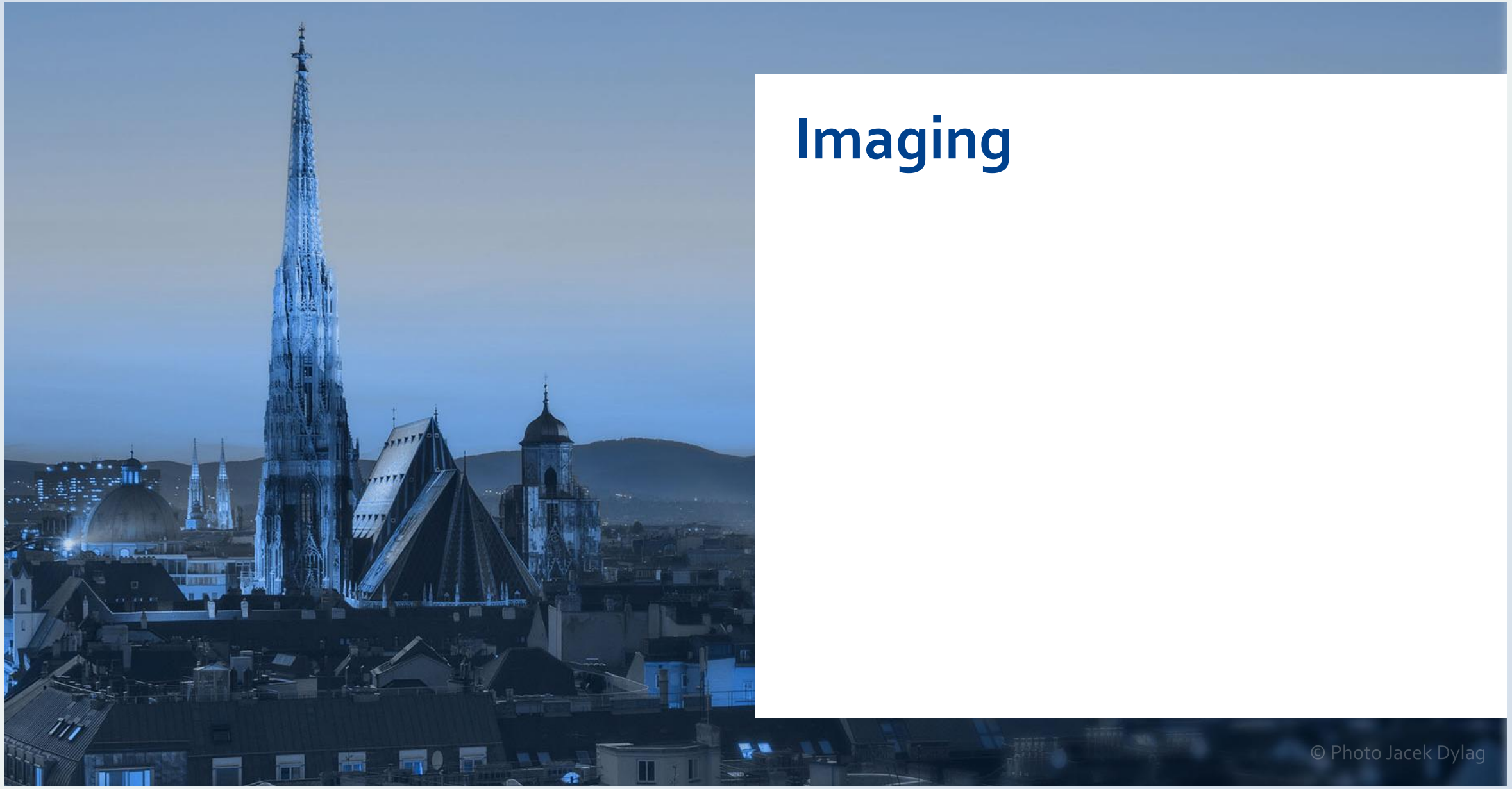


AUC, area under the curve; **NET**, neuroendocrine tumor; **SI-NET**, small intestinal neuroendocrine tumor; **SSA**, somatostatin analog; **TBR**, tumor to background ratio.
1. Bertani E et al. ENETS 2024; Jo5. 2. El Lakis M et al. JAMA Surg. 2019; 154(1): 40-45.

Experts' comments

- Surgical management of NET ranges from conservative to extended surgical resection based on tumor size and location. More than one-third of patients with NET present with distant metastases, with the liver being the most common site of distant metastasis.
- New treatment options for liver metastases, including SIRT and portal vein resection, are being tested alongside other methods, such as ablation or embolization.
- Radio-guided surgery with new probes is a novel approach focused on providing surgeons with a clearer delineation of the margins of lesions.

NET, neuroendocrine tumor; **SIRT,** selective internal radiotherapy.



Imaging

PET/CT imaging of SSTR2 with [18F]AlF-OC PET/CT: Impact on tumor staging and therapeutic management

^{68}Ga-DOTA-SSA PET/CT is considered the current gold standard for NET diagnosis and staging, but availability is limited because of practical and economic issues

^{18}F production is more available and cheaper, [18F]AlF-OC was previously shown to be a feasible tracer for NET[1]

A multicenter trial in 75 patients with histologically confirmed NET

Aim:
To demonstrate non-inferiority of [18F]AlF-OC to [68Ga]-DOTA-SSA

Results

No difference in TNM staging and therapy choice in 65/75 patients (86.7%)

7 patients were up-staged

3 were down-staged

For 7 patients, treatment was escalated

Conclusions

- Additional lesion detection when using [18F]AlF-OC
- Only limited impact on patient management
- [18F]AlF-OC should be incorporated in guidelines and reimbursed

68Ga, gallium-68; **18F**, fluorine-18; **NET**, neuroendocrine tumor; **OC**, octreotide; **PET/CT**, positron emission tomography/computed tomography; **SSA**, somatostatin analog; **SSTR**, somatostatin receptor; **TNM**, tumor, nodes, metastasis.

Leupe H et al., ENETS2024:H08; 1 Pauwels E et al., J Nucl Med. 2023 Apr;64(4):632-638.

The role of functional imaging in predicting the risk of post-operative recurrence of panNET

- Recurrence rate in panNET is up to 50% and there are no published data on the prognostic value of functional PET imaging
- A retrospective study in 157 patients who underwent surgery for non-metastatic panNET and had a baseline ^{68}Ga-PET
- A multivariate model was performed to obtain prognostic factors with the goal of creating predictive nomograms that include both pathologic and radiologic terms
- From the 3-year prediction of recurrence nomograms, the AUCs were
  - Pre-operative model: 0.77 [0.645-0.88]
  - Post-operative model: 0.86 [0.76-0.95]
- Pre-operative PET imaging parameters, combined with clinicopathological factors, increased the prognostic stratification of patients with non-metastatic sporadic panNET; However, validation by other centers is necessary

Disease-free survival at 3 years was 83%.

Pre-operative model

Variable	HR [95% CI]	p
Age (by 5 years)	1.13 [0.97; 1.32]	0.114
Tumoral volume (mm3) (by 1, log)	1.48 [1.11; 1.98]	0.008
SUV max (log)	2.10 [1.24; 3.55]	0.006

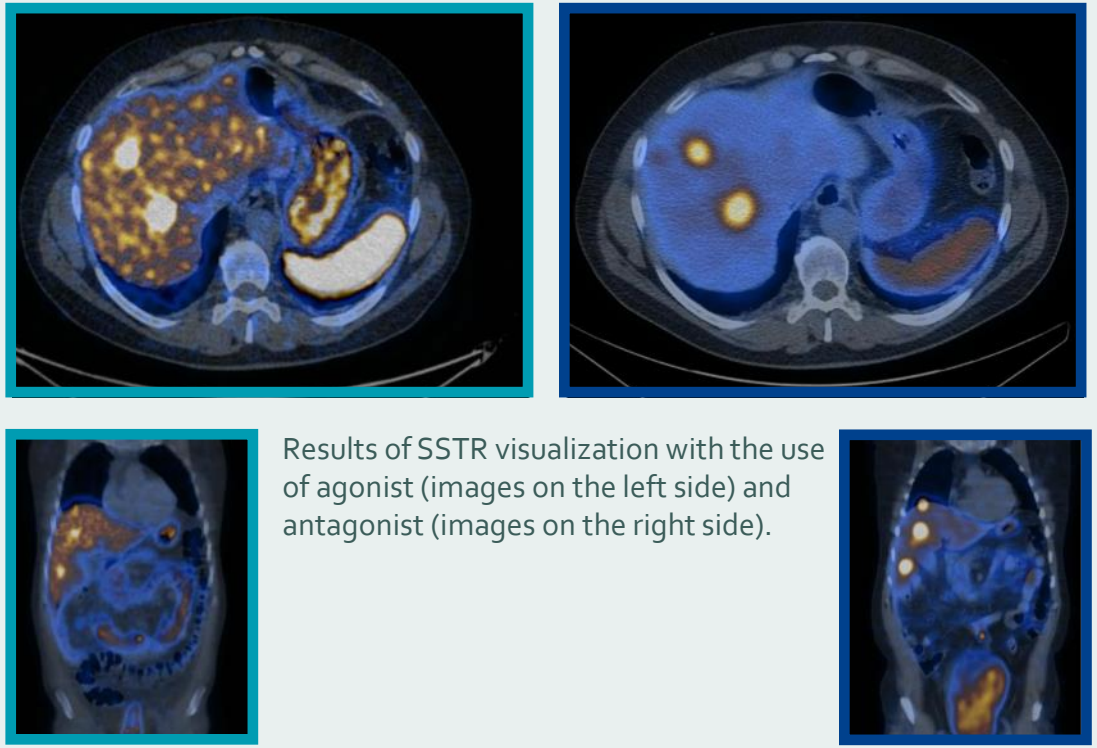
Post-operative model

Variable	HR [95% CI]	p
Ki67 (by 1)	1.05 [1.00;1.10]	0.045
SUV max (log)	2.48 [1.25; 4.92]	0.009
Log2 (Joint entropy) (by 1)	1.16 [0.94; 1.43]	0.170
Vascular invasion	2.09 [0.81;5.34]	0.125

^{68}Ga, gallium-68; **AUC**, area under the curve; **NET**, neuroendocrine tumor; **PET**, positron emission tomography; **panNET**, pancreatic neuroendocrine tumor; **SUV**, standardized uptake value.
De Mestier L et al., ENETS2024:J16

TECANT ERA PerMed study: Could SSTR antagonists (SSTRa) be a new sensitive diagnostic tool for reliable assessment of SSTR status in NEN?

- NEN imaging with SSTRa promises to be a useful tool in the future, as SSTRa recognizes more binding sites on their target
- 99Tc-based tracers could improve access to this clinically feasible diagnostic tool
- This study set out to assess the safety and tolerability of the ^{99m}Tc-labelled SSTR2a [99mTc]Tc-TECANT1 in patients with NEN and its capacity to detect tumors in SPECT/CT imaging
- Results:
  - Imaging was performed in 10 patients, with no IMP-related adverse effects
  - [99mTc]Tc-TECANT1 tumor uptake was visible at 5 min and was retained up to 24 h post-injection
  - NEN lesions were highly visible in all scanned patients, with most lesions having better contrast compared to images obtained with ^{68}Ga-based SSTR agonists
- SSTRa imagines provide a better tumor-to-background ratio which may lead to improved staging and treatment outcomes



Results of SSTR visualization with the use of agonist (images on the left side) and antagonist (images on the right side).

^{68}**Ga,** gallium-68; ^{99}**Tc,** technetium-99; **IMP,** investigational medicinal product; **NEN,** neuroendocrine neoplasm; **SPECT/CT,** single-photon emission computed tomography/ (X-ray) computed tomography; **SSTR,** somatostatin receptor.
Opalinska M et al, ENETS2024:H15

^{68}Ga-DOTANOC and ^{18}F-FDG PET/CT in predicting the prognosis of patients with metastatic RNET

- Rectal NET (RNET) is the second most common NET after panNET in the Chinese population
- This study aimed to evaluate the prognostic power of ^{68}Ga-DOTANOC and ^{18}F-FDG PET/CT for patients with RNET
- 235 patients with RNET who underwent ^{68}Ga PET/CT at baseline were investigated from July 2021 to December 2023

Results

- 74 patients with metastatic RNET were enrolled
  - Of these, 46 had additionally received ^{18}F-FDG PET/CT in the 7 days before or after the ^{68}Ga scan
- ^{68}Ga and ^{18}F scans identified tumors in 98.6% and 28.3% of patients, respectively; Ki-67 of ^{18}F-positive tumors was mostly >10%
- ^{18}F positivity was a factor for PFT independent of ^{68}Ga positivity

Conclusions

- ^{18}F-FDG PET/CT is an independent predictor for prognosis in RNET patients
- Diffuse liver metastasis assessed by ^{68}Ga-DOTATOC PET/CT is another risk factor in RNET

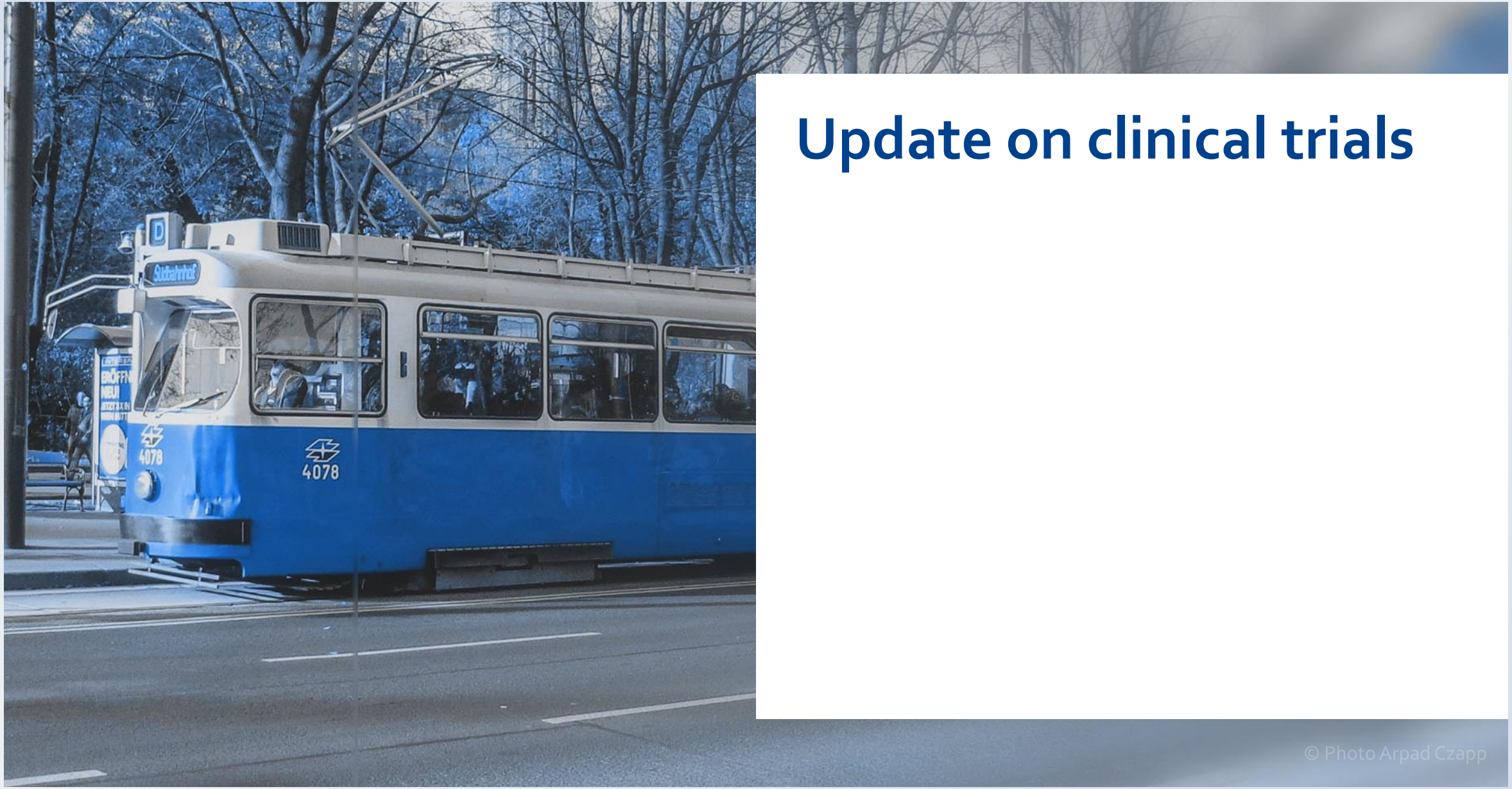
^{18}F, fluorine-18; **^{68}Ga,** gallium-68; **CT,** computed tomography; **FDG,** fluorodeoxyglucose; **NET,** neuroendocrine tumor; **PET,** positron emission tomography; **panNET,** pancreatic neuroendocrine tumor; **RNET,** rectal neuroendocrine tumor.

Xu J et al., ENETS2024:H26

Experts' comments

- PET imaging, combined with cross-sectional imaging, is crucial for accurately diagnosing and staging cancer patients and may provide additional information to guide optimal treatment decisions. Yet radionuclides needed for PET imaging are difficult to produce and are expensive.
- Novel tracer options need to be considered and tested, e.g., [18F]AlF-OC, which is considerably cheaper and easier to produce without being inferior to well-characterized tracers such as [68Ga]-DOTA-SSA. Using SSTR antagonists instead of agonists could potentially increase imaging contrast due to their higher binding site recognition on the target cells. The advancements in radiotracers could benefit patients in countries with access to them.
- In some cases, using a combination of different imaging techniques or radiotracers can provide a more comprehensive view of the disease.

PET/CT, positron emission tomography/ computed tomography; SSA, somatostatin analog; SSTR, somatostatin receptor



Update on clinical trials

Updated data from a phase I trial of the DLL3/CD3 IgG-like T-cell engager BI 764532 in patients with DLL3-positive (+) tumors: Focus on epNECs

Background

- BI 764532 is a novel CD3/DLL3 bispecific T-cell engager
- NCT04429087 is a first-in-human dose escalation trial of BI 764532 in patients with SCLC or epNECs
- Open for patients with DLL3-expressing tumors that did not respond to chemotherapy, with adequate organ function and ECOG PS 0/1
- 150 patients recruited (epNEC n=66)
- Endpoints: MTD, DLTs (primary); Objective response, PK parameters (secondary)

Safety

- DLT: 7 in total; thereof 1 case of G5 ICANS and 1 of G3 CRS in patients with epNEC
- ≥G3 TRAEs were:
  - Lymphopenia (11%)
  - CRS (3%)
  - CRS (2%)
- CRS occurred mainly during early administrations and was manageable with step-in dosing and supportive care

Efficacy

- Patients with epNEC experienced PR, SD and PD at rates of 22%, 19% and 43%, respectively
- All PRs occurred at doses ≥90 µg
- Responses were best in epNECs of the genitourinary system
- The 6-month DoR rate was 62%

Conclusion

- Safety profile was acceptable with mostly G1-2 TRAEs
- Promising efficacy in epNEC: ORR of 26% at doses of ≥90 µg

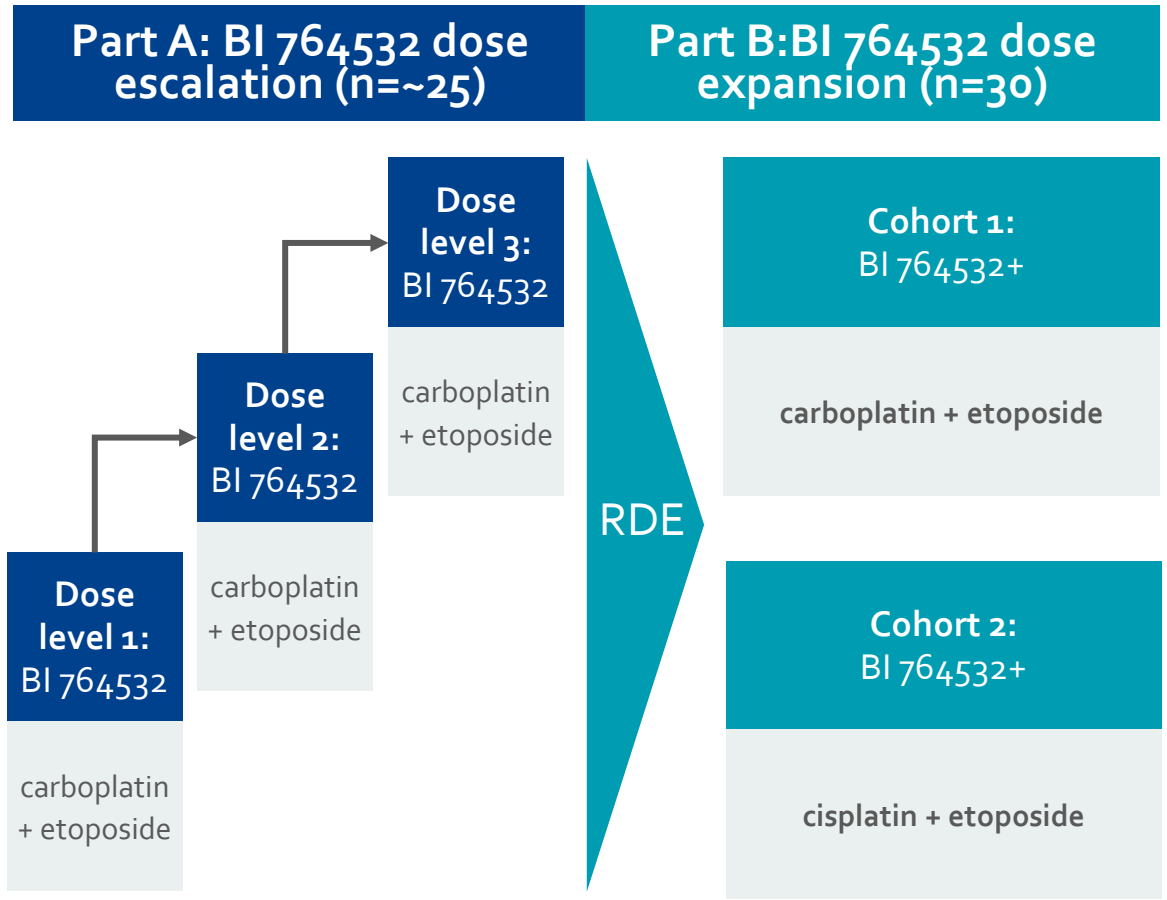
CD3, cluster of differentiation 3; **CRS,** cytokine release syndrome; **DLL3,** delta-like ligand 3; **DLT,** dose-limiting toxicity; **DoR,** duration of response; **ECOG PS,** Eastern Cooperative Oncology Group performance score; **epNEC,** extra-pulmonary neuroendocrine cancer; **G,** grade; **ICANS,** immune cell-associated neurotoxicity syndrome; **IgG,** immunoglobulin G; **MTD,** maximum tolerated dose; **ORR,** objective response rate; **PD,** progressive disease; **PK,** pharmokinetics; **PR,** partial response; **SCLC,** small cell lung cancer; **SD,** stable disease; **TRAE,** treatment-related adverse event.

Capdevila J et al., ENETS2024:103

DAREON -7: A Phase I, open-label, dose escalation and expansion cohort trial of BI 764532 + platinum in patients with DLL3-positive NEN

- DAREON-7 will be a clinical trial on the combination of conventional chemotherapy with platin/etoposide (p/e) and the novel T-cell engager BI 764532

Two-part design	Part A	Part B
Description	Dose escalation	Dose expansion
Enrollment target; N	25	30
Objectives	MTD and/or RP2D + dose-tolerability relationship	Confirm safety and tolerability of p/e + BI 764532 at RP2D
Endpoints	Occurrence of DLTs	Occurrence of DLTs, objective response (defined as best overall response of CR or PR, DoR)



CR, complete response; **DLT,** dose-limiting toxicity; **DoR,** duration of response; **MTD,** maximum tolerated dose; **NEN,** neuroendocrine neoplasm; **RP2D,** recommended phase 2 dose; **PR,** partial response.
Capdevila J et al., ENETS2024:M02

Preliminary pilot study results from COMPOSE

- COMPOSE*, a Phase III study of RPT Lu-edotreotide vs. SOC in well-differentiated, grade 2/3, SSTR+ GEP-NETs, offered an optional genomic profiling sub-study to identify prognostic biomarkers and to predict RPT response
  - Participation in the sub-study did not affect the disease management or trial procedures
- The pilot study aims were reached, demonstrating that the experimental approach of the genomic profiling sub-study is robust
  - 130 patients completed data sets as expected
  - Operational aspects of the trial were successful
  - Clinical samples were of good quality
  - Sequencing parameters were appropriate

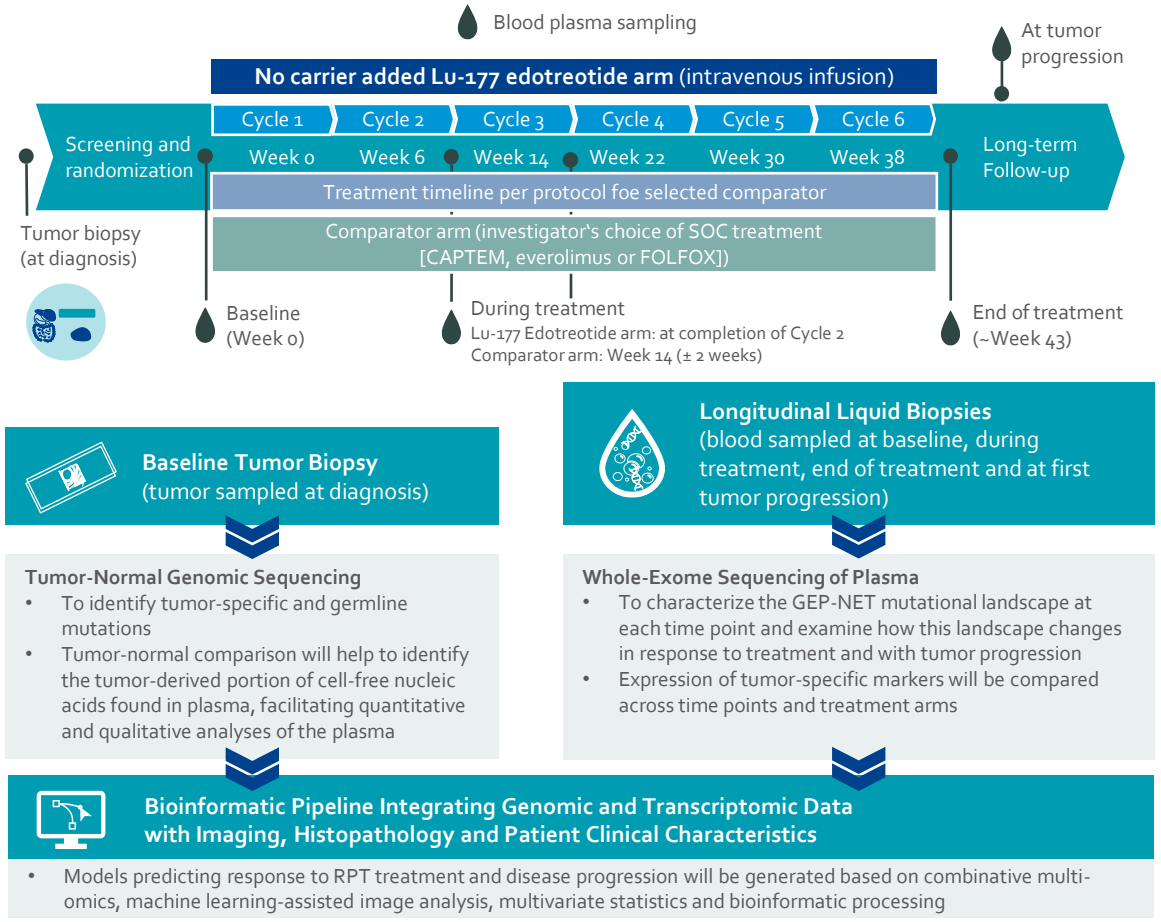
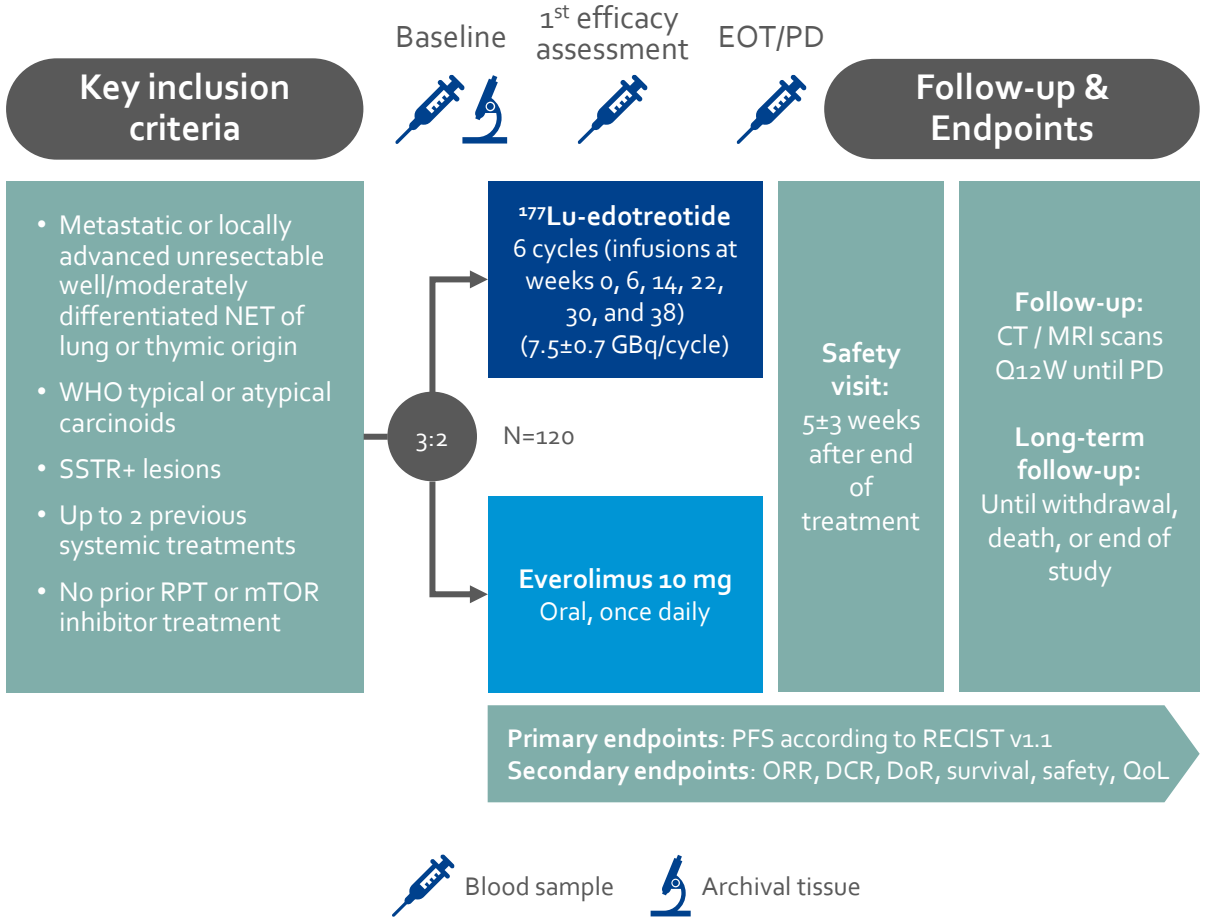


Figure: COMPOSE genomic sub-study design. *NCT04919226
CAPTEM, capecitabine and temozolomide; **FOLFOX,** folinic acid, fluorouracil and oxaliplatin; **GEP-NET,** gastroenteropancreatic neuroendocrine tumor; **Lu-177,** lutetium-177; **RPT,** radiopharmaceutical therapy; **SOC,** standard of care; **SSTR,** somatostatin receptor.
Srirajaskanthan R et al., ENETS 2024:M12

RPT tested in advanced lung and thymic NETs

- Treatment options are limited for patients with advanced lung and thymic NETs
- Everolimus is the only approved drug for this patient population, and there is an urgent unmet need for alternative treatments
- Approximately 50%-70% of lung NETs express SSTR2 and could be potentially treated using RPT
- LEVEL*, a Phase 3 study of RPT Lu-Edotreotide vs. everolimus in progressive, advanced, well-/moderately differentiated NETs of lung or thymic origin, received institutional review board/ethics committee approval
- Recruitment started in October 2023 and the study has already recruited 16 patients
- An interim analysis will be conducted after 60 PFS events



177Lu, lutetium-177; **CT**, computed tomography; **DCR**, disease control rate; **DoR**, duration of response; **EOT**, end of treatment; **MRI**, magnetic resonance imaging; **mTOR**, mammalian target of rapamycin; **NET**, neuroendocrine tumor; **ORR**, objective response rate; **PD**, progressive disease; **PFS**, progression-free survival; **Q12W**, every 12 weeks; **QoL**, quality of life; **RPT**, radiopharmaceutical therapy; **SSTR**, somatostatin receptor; **WHO**, World Health Organization.

García-Álvarez A. ENETS 2024:M05

*NCT05918302

ACTION-1: ^{225}Ac-DOTATE (RYZ101) in SSTR2+ well-differentiated GEP-NETs with progression following ^{177}Lu-SSA

Key eligibility criteria

- Age ≥18 years
- Histologically proven, G1-G2, well-differentiated, advanced GEP-NETs
- Ki-67 ≤20%
- Progressive GEP-NET based on RECIST v1.1 (centrally confirmed) after 2-4 cycles of ^{177}Lu-SSA (must have had disease control for at least 6 months after ^{177}Lu-SSA)
- RECIST v1.1 measurable SSTR+ disease within 4 weeks prior to randomization and no RECIST measurable SSTR- metastatic disease
- ECOG performance status ≤2
- CrCl ≥60 mL/min
- No prior radioembolization

Randomized treatment phase

R 1:1

RYZ101 at 10.2 MBq Q8W x 4

Investigator's choice SoC[a]
everolimus or
sunitinib or
high-dose long-acting SSA

[a]Crossover to RYZ101 following centrally confirmed disease progression is permitted.

Endpoints

Primary
- PFS (per BICR)

Secondary/exploratory
- OS
- ORR
- BOR, DoR
- DCR
- Safety
- PFS2
- Biomarkers (incl. CgA, 5-HIAA)
- HRQoL: EQ-5D-5L, EORTC C30, EORTC QLQ GI NET21
- PK: exposure, relationship with efficacy and safety

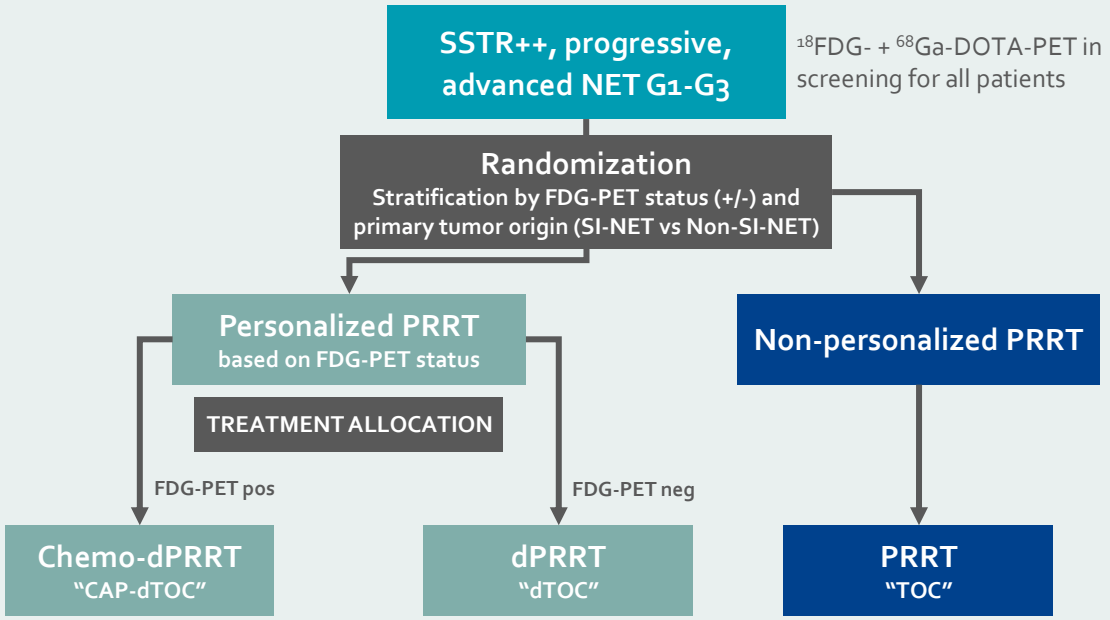
! Part 2 (Phase 3) of the ACTION-1 trial is currently enrolling and is planned at ~80 sites in North America, South America, Europe and Asia.

^{177}Lu, lutetium-177; **^{225}Ac,** actinium-225; **5-HIAA,** 5-hydroxyindoleacetic acid; **BICR,** blinded independent central review; **BOR,** best overall response; **CgA,** chromogranin A; **CrCl,** creatinine clearance; **DCR,** disease control rate; **DoR,** duration of response; **ECOG,** Eastern Cooperative Oncology Group; **EORTC,** European Organisation for Research and Treatment of Cancer; **G,** grade; **GEP-NET,** gastroenteropancreatic neuroendocrine tumor; **GI,** gastrointestinal; **HRQoL,** health-related quality of life; **ORR,** objective response rate; **OS,** overall survival; **PFS,** progression-free survival; **PFS2,** PFS after 1st subsequent anticancer therapy; **PK,** pharmacokinetics; **Q8W,** every 8 weeks; **QLQ,** quality of life questionnaire; **R,** randomised; **RECIST,** Response Evaluation Criteria In Solid Tumors; **SoC,** standard of care; **SSA,** somatostatin analogue; **SSTR,** somatostatin receptor. 1. Singh S et al. ENETS 2024; M10

Phase 3 trial to compare personalized vs. non-personalized RPT

- RPT for advanced NETs is given as a fixed activity dosing protocol, but emerging data suggests that aggressive NETs may benefit from personalized treatment, like combining RPT with chemotherapy
- Dosimetry can be used to increase the tumor radiation doses without surpassing the toxicity limits of at-risk organs
- START-NET*, an academic phase III study in SSTR+, advanced, progressive NET G1-G3 (Ki-67<50%), randomly assigned patients fixed-dose (control) or personalized treatment based on FDG scan results[1]
  - FDG-negative received dosimetry-based RPT
  - FDG-positive received capecitabine + dosimetry based RPT
  - Primary endpoint was PFS; N=300; trial status ongoing
- CORONET, another phase III trial, currently under assessment, evaluating CAPTEM/RPT vs. RPT in patients with G2/G3 panNET (FDG + or -) and who are deemed suitable for RPT[2]

START-NET study design



TOC: 4 x 7.5 GBq ^{177}Lu-DOTATOC. Cycle interval 10 ± 2 weeks.
dTOC: X cycles of 7.5 GBq ^{177}Lu-DOTATOC to a renal AD ≤ 30 Gy. Cycle interval 10 ± 2 weeks.
CAP-dTOC: 4 x 7.5 GBq ^{177}Lu-DOTATOC + CAPECITABINE followed by X cycles of 7.5 GBq ^{177}Lu-DOTATOC to a renal AD ≤ 30 Gy. Cycle interval 10 ± 2 weeks.

AD, absorbed dose; **CAPTEM**, capecitabine and temozolomide; **FDG**, fluorodeoxyglucose; **G**, grade; **NET**, neuroendocrine tumor; **PET**, positron emission tomography; **PFS**, progression-free survival; **panNET**, pancreatic neuroendocrine tumor; **PRRT**, peptide receptor radionuclide therapy; **RPT**, radiopharmaceutical therapy; **SI**, small intestine; **SSTR**, somatostatin receptor.

1. Asp P. ENETS 2024:M01. 2. Chan DL. ENETS 2024:M03; *NCT05387603

Experts' comments

- New T-cell redirecting strategies, such as bi-specific T-cell engager (BiTE), have become an attractive and promising option for further developing immunotherapy in a more selected, biomarker-driven NEN patient population.
- In addition to the data presented for the NETTER-2 trial, the results of three other phase 3 trials testing a non-carrier-added (n.c.a.) RPT version in ^{177}Lu-Edotreotide is being tested in lung and GEP-NETs. The results from these trials may lead to a broader application of RPT soon, especially in lung NET and higher-grade GEP-NET.
- In addition, due to the promising results of ^{225}Ac-PSMA treatment in metastatic castrate-resistant prostate cancer, α-emitting SSTR-targeting drugs have also become attractive in the NET setting.
- Currently, RPT for advanced NETs is given as a fixed activity dosing protocol of four cycles of 7.4 GBq, eight weeks apart. Trials are ongoing to test the benefit of personalized dosimetry-based treatment.

NET, neuroendocrine tumor; **RPT,** radiopharmaceutical therapy; **SSTR,** somatostatin receptor.

Helpful tips for supporting patients

The NUTRIGETNE Study assessed the impact of nutritional status on the QoL of patients with advanced GEP-NEN

- Patients with GEP-NEN often suffer from malnutrition and sarcopenia[1-3], which impacts their prognosis and QoL[4,5].
- A study from Spain assessed the impact of nutritional status on QoL-related patient-related outcomes in patients with advanced GEP-NEN
- Malnutrition and sarcopenia affected 61.9% and 15% of patients, respectively
- Malnutrition and sarcopenia correlated with higher rates of fatigue, appetite loss, overall QoL and impacted physical performance
- **Conclusion:** Malnutrition and sarcopenia have a high prevalence and negatively impact the QoL of patients with advanced GEP-NEN

GEP-NEN, Gastroenteropancreatic neuroendocrine neoplasm; **NET**, neuroendocrine tumor; **QoL**, quality of life.

Olmo-García M et al., ENETS2024:D21; 1. Clement M et al. J Gastroenterol. 2019; 2. Altieri B et al. Rev Endocr Metab Disord.2018; 3. Laing E et al. Neuroendocrinology. 2020; 4 Maasberg S et al. Neuroendocrinology. 2017; 5. Barrea L et al. Nutrients. 2018

Management of insulinomas

- Insulinomas are functional NETs, arising from β-cells in the pancreas and can cause hyperinsulinism
- Patients suffer from low hypoglycemia, which can be alleviated by ingesting carbohydrates; this can be guided with continuous glucose monitors
- Hyperinsulinism can decrease after successful therapy, necessitating adjustment to the diet
- Previously diabetic patients may again require anti-diabetic medication and/or insulin injections

Dietitian's advice for patients with hypoglycemia: Treatment escalation

1. Ingestion of 1 g/kg body weight every 4-6 hours
2. Uncooked corn starch, suitable for nocturnal hypoglycemia
3. Glycosade (modified high amylopectin corn starch): slow release, higher intake possible
4. Artificial feeding: In severe cases, patients must be fed carbohydrates via a feeding tube

NET, neuroendocrine tumor.
Ho, T-W et al., ENETS2024

Prevalence of depressive and anxiety symptoms and disorders in NEN: A systematic review and meta-analysis

Background and Methods

- Patients and survivors of NEN are at a significant risk of depression and anxiety
- The prevalence of these conditions within the NEN population remains unknown
- A Chinese study searched through databases for different studies that recorded the prevalence of depression/anxiety in patients with NEN

Results

- 28 studies with 12,272 participants were included in this review
- The odds of having depressive symptoms were higher among patients with NEN (n=15 studies; OR 1.34; 95% CI: 1.21 to 1.47).
- Patients with NEN had higher odds of experiencing anxiety symptoms (n=14 studies; OR 1.37; 95% CI: 1.19 to 1.57).

Conclusions

- The increased risk of depression and anxiety among patients with NEN should be considered during treatment

Limitations

- The methodological quality of the included studies was moderate to low
- There was substantial heterogeneity in symptoms between studies

CI, confidence interval; **NEN**, neuroendocrine neoplasm; **NET**, neuroendocrine tumor; **OR**, odds ratio.
Chen XY et al., ENETS2024:D14

Group therapy for those living with a neuroendocrine neoplasm (NEN) diagnosis: A utility evaluation

?

The demand for psychotherapy and counseling services by far exceeds the capacity; group therapy can be a cost- and outcome-efficient alternative to individualized options.

...

An expert facilitated pilot program tested the concept of group therapy in patients with NEN. Patients attended weekly for 8 weeks. 11 patients participated long-term.

!

After the program, 100% of attendees reported feeling better equipped to manage their mental health and well-being. Everyone who participated in the program said they would recommend it to others.

Implementation of a new, nurse-led clinic (NLC) for patients with NET

- Nurse-led clinics could be a cost-efficient way of improving care for patients with NET, a group with higher-than-average symptom burden
  - This approach is supported by international evidence
- This study established a pilot clinic for patients with G1/G2 NET on "watchful waiting" or SSA treatment
- Frequency of clinic visits per patient was determined by a supervising oncologist; clinical escalation policies were put in place for safety
- 71 NLC consultations were conducted over 6 months, thereof 18 in person and 53 via telehealth
- Future directions: This clinic model has been expanded since the pilot and the range of offered services expanded
- Expansion of the service has been approved

Conclusions

- Evaluation is ongoing, but preliminary anecdotes from patients were collected
- Anecdotally, very high levels of patient satisfaction, with patients appreciating the opportunity to receive specialist nursing input
- Cost-effective model of care
- Model of care acceptable to supervising Medical Oncologist and hospital leadership

G, grade; **SSA**, somatostatin analog.
Wakelin K et al., ENETS2024:No2

Co-production of patient information: A model for today's practice

?

Background: Patient-centered information is critical; patients are considered partners in their care. Liver transplantation has recently been re-introduced for patients with NEN and quality information on the subject is essential.

...

Aim: To produce an information resource for patients and their families on liver transplantation for patients with NEN-related liver metastases.
Method: Discussions and workshops were held with patients, their families, and advocates; a working group was established which included patients who received or are eligible to receive a liver transplant and expert nurses.

!

Results: A finalized version was approved by all parties in August 2023, published on the charity's website during *Transplantation Awareness Week* and is being adopted as the national patient information resource for the program.

NEN, neuroendocrine neoplasm.
Jervis N and Bouvier-Ellis N, ENETS2024:N01

Education initiatives for non-NEN HCPs

INCA (International Neuroendocrine Cancer Alliance) – Think NEN program for PCP education

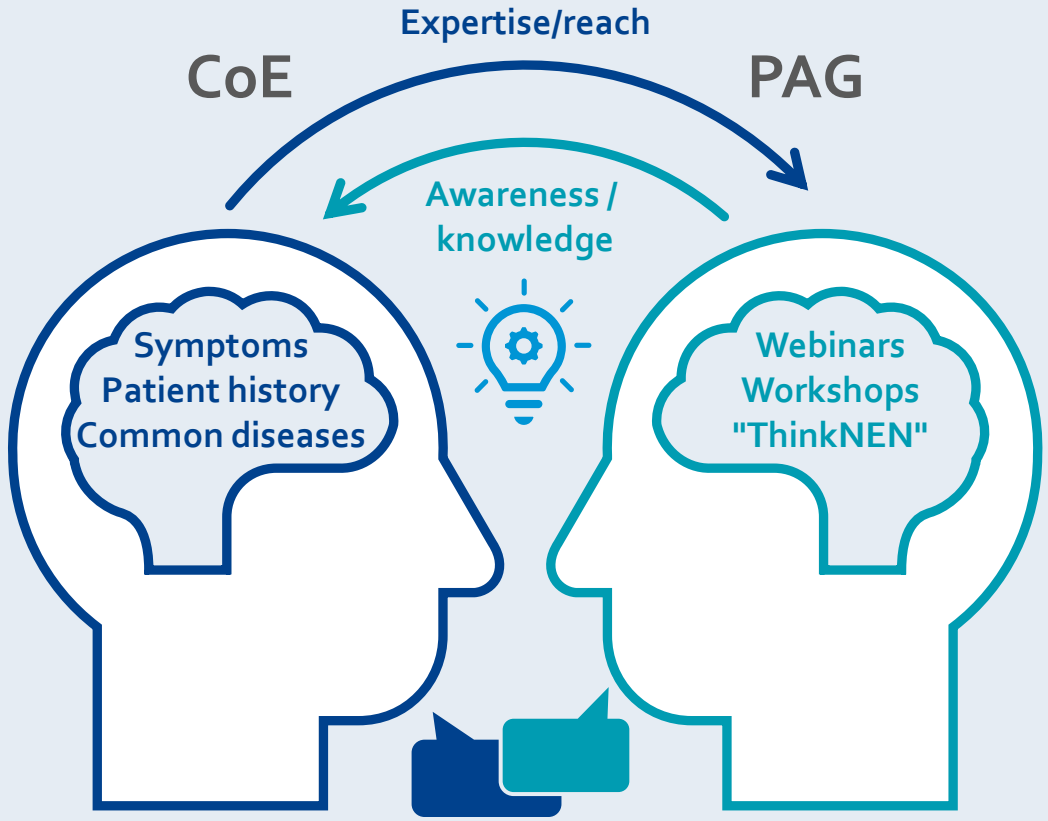
- Patients with NET are often misdiagnosed
  - >50% have stage 4 cancer at diagnosis
- Educational Goals:
  - Diagnostic awareness
  - Diagnostic pathways
  - Managing patients in the community
- Offers a variety of educational videos, workshops, courses

NeuroEndocrine Cancer Australia

- Offers free, online, educational material on NEN
- Modules:
  - 1 – Suspecting NET in General practice
  - 2 – Medical Management
  - 3 – Specific NETs
  - 4 – Living with NETs
- 3,708 HCPs have participated

HCP, healthcare professional; **NEN,** neuroendocrine neoplasm; **NET,** neuroendocrine tumor; **PCP,** primary care physician.
O'Toole D, ENETS2024; Kolarova T, ENETS2024; Cummins M, ENETS2024

Enganging second-line non-NEN HCPs



- A major problem is rare diseases are care systems as pathways are not aligned for most people with rare diseases due to a lack of awareness and knowledge
- What needs to happen?
  - PAGs and CoEs need promote knowledge and awareness
  - Available financial resources must be used (the total financial support for all rare diseases is substantial!)
  - Use of AI to facilitate symptom pattern recognition
- Conclusions
  - The market of attention is competitive
  - NET advocacy groups are crucial, and patients must be empowered
  - Change of mindset is needed: NET is not a rare disease
  - AI could greatly help, and NET would be an excellent disease to pilot AI-driven diagnosis

AI, artificial intelligence; **CoE,** cluster of excellence; **ER,** emergency room; **HCP,** healthcare professional; **NEN,** neuropendocrine neoplasm; **NET,** neuroendocrine tumor; **PAG,** patient advocacy group.
Caplin M, ENETS2024

Experts' comments

- Comprehensive management of NEN should cover all aspects including nutrition, psychological support, and involvement of healthcare professionals who are not NEN experts.
- The initial findings of a broad nutrition evaluation study revealed a significant prevalence of malnutrition and sarcopenia, which should be actively assessed and effectively managed.
- There is a need to raise awareness about NEN diseases among healthcare professionals outside of the hospital setting for early detection and ongoing management.

THERANOSTICS

Appendix

Photo: Marie Rouffy

Meet the consulting experts

Jaume Capdevila
Oncologist
Vall d'Hebron University Hospital
Barcelona, Spain

Jaume Capdevila is a Professor in the Medical Oncology Dept at the Vall d'Hebron University Hospital and Senior Researcher at Vall Hebron Institute of Oncology.

He is the current Chair of the Spanish Task Force for Neuroendocrine and Endocrine Neoplasms (GETNE) and the current member of the ENETS Executive Committee for Spain.

He has also served as ENETS Executive Committee and Advisory Board Member.

Wouter de Herder
Endocrinologist
Erasmus MC
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Wouter de Herder is a Professor of Endocrine Oncology at the Department of Internal Medicine at Erasmus MC Rotterdam Cancer Center.

He was the Chair of ENETS (2006-2008) and the Chair of the ENETS Advisory Board (2015-2018).

He has also served as the Head of the ENETS Center of Excellence at the Erasmus MC Rotterdam Cancer Center.

Disclosures

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THERANOSTICS

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