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Advancing the multidisciplinary management of rare and unusual NETs: Integrating new approaches to treatment and care

Multidisciplinary panel

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Achieving a NET/NEC diagnosis: Ongoing challenges

Low index of suspicion among patients and HCPs[1]

Of 17% SCPs suspecting cancer, only 1 in 5 suspect NET/NEC[1]

Frequent initial misdiagnosis[1]

Nearly half (44%) of patients initially misdiagnosed[1]

Lack of NET/NEC specialist pathways[1,2]

Patients see 6 HCPs on average before receiving a diagnosis[2]

Limited access to latest diagnostic tools[1]

Most patients report limited access to ^{68}Ga-PET/CT scanning facilities

Improving diagnosis is a patient priority[3]

~1 in 4 patients receive NET/NEC diagnosis following initial presentation[1]

Misdiagnosed patients waited 5 years for accurate diagnosis; 81% still not accurately diagnosed ≤1 year[1]

Most patients receive a stage IV diagnosis[3] (Europe – 55%; North America - 61%)

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Clinical case 1: Lung NET

Presentation

- 41-year-old female with a history of chronic cough and intermittent wheezing

- Reports often feeling fatigued, but no other symptoms
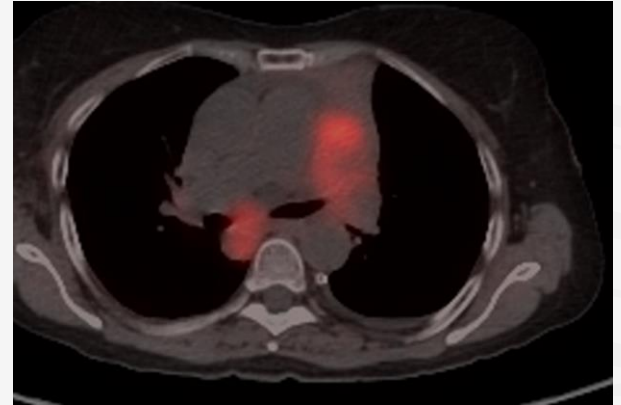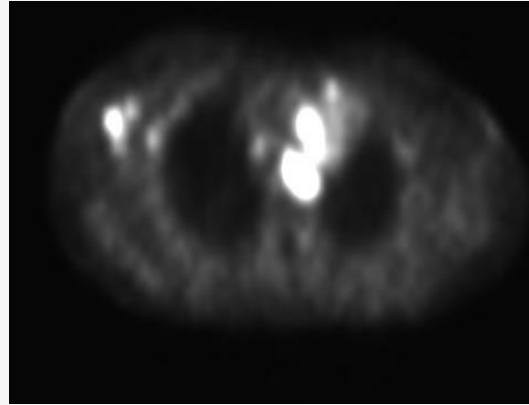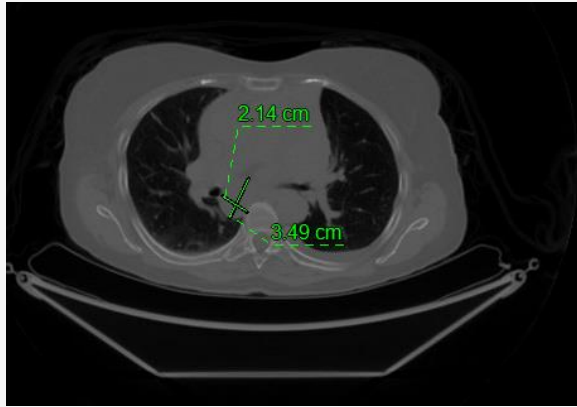
Findings from further investigations

- Bronchopulmonary NET atypical carcinoid, Ki67 30%
- Positive for synaptophysin, chromogranin, CD56, INSM1, TTF-1, and Rb retained
- p53 wild-type expression

PET dotatate scan results:
- Metastatic with tracer avid b/l SCLN (SUV 2.1), left perihilar/hilar (SUV 8.2), pleural lesions (SUV 7.5), moderate pleural effusion, left thoracic inlet 2.8x2.1 cm (SUV 8), left prevascular (SUV 8.1)
- Liver: No abnormal uptake
- Bones: Right base skull (SUV 3.3), right iliac wing SUV 2.1, right supra-acetabular (SUV 3), right posterior acetabulum (SUV 1.4)

b/l, bilateral; CD56, neural cell adhesion molecule; INSM1, insulinoma-associated protein 1; NET, neuroendocrine tumour; PET, positron emission tomography; Rb, retinoblastoma; SCLN, supraclavicular lymph node; SUV, standardized uptake value; TTF-1, thyroid transcription factor-1.

Clinical case 1: Lung NET

NET, neuroendocrine tumour.
Images provided courtesy of Dr Diane Reidy Lagunes.

Clinical case 1 (lung NET): Trial data

Study	Population	Regimen	Key clinical outcomes
SPINET[1,2] Phase III RCT (NCT02683941)	**Well differentiated, metastatic and/or unresectable, atypical or typical, BP-NETs (N=77)**	**Lanreotide (autogel) plus BSC (n=51)** vs PBO plus BSC (n=26)	mPFS, months (95% CI): **16.6** (12.8–21.9) vs 13.6 (8.3–NC) HR (95% CI): **0.90** (0.46–1.88)
			mPFS (by carcinoid type), months (95% CI): Typical: **21.9** (12.8–NC); atypical: **14.1** (5.6–16.6)
			Serious AEs, %: **19.6** (n=10) vs 26.9 (n=7) AEs leading to withdrawal: **3.9** (n=2) vs 11.5 (n=3)
RADIANT4[2,3] Phase III RCT (NCT01524783)	**Primary LNET subgroup (N=90)**	**Everolimus plus BSC (n=63)** vs PBO plus BSC (n=27)	mPFS (central review), months (95% CI): **9.2** (6.8–10.9) vs 3.6 (1.9–5.1) HR (95% CI): 0.50 (0.28–0.88)
			≥1 dose adjustments, %: **69.4** (n=43; mostly due to AEs) vs 29.6 (n=8)
CAPTEM[4] Single-centre retrospective study	**Metastatic lung NENs incl. NET (typical and atypical) and LCNEC (N=20; consecutively treated)**	**Capecitabine / Temozolomide**	**85% DCR**; BoR: **30% PR, 55% SD** mPFS, months (95% CI): **13** (4.4–21.6); mOS, months (95% CI): **68** (35.3–100.7)
			AEs: mostly grade 1; grade 4 thrombocytopenia in 2 patients No discontinuations due to drug-induced toxicity
CABINET[2] Phase III RCT (NCT03375320)	**Advanced NETs following progression on prior therapy (incl. LNETs) (N=~395)**	**Cabozantinib** vs PBO	Primary endpoint: PFS *RECRUITING* Estimated completion date October 2025
Alliance A021901[2] Phase II RCT (NCT04665739)	**SSTR-positive advanced bronchial NETs (N=~108)**	**[177]Lu-DOTATATE** vs everolimus	Primary endpoint: PFS *RECRUITING* Estimated completion date July 2024

AE, adverse event; BP-NET, bronchopulmonary NET; BoR, best overall response; BSC, best supportive care; CI, confidence interval; DCR, disease control rate; HR, hazard ratio (progression or death); LCNEC, large cell neuroendocrine carcinoma; LNET, lung NET; m, median; NC, not calculable; NEN, neuroendocrine neoplasm; NET, neuroendocrine tumour; OS, overall survival; PBO, placebo; PFS, progression-free survival; PR, partial response; RCT, randomized controlled trial; SD, stable disease; SSTR, somatostatin receptor.

1. Horsch D, et al. *Ann Oncol.* 2021;32(Suppl. 5):S906–20; 2. ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/home (accessed 30 Aug 2022); 3. Fazio N, et al. *Cancer Sci.* 2018;109:174–81; 4. Al-Toubah T, et al. *The Oncologist.* 2020;25:e48–52.

Clinical case 2: NET with liver-dominant disease

Presentation

- 53-year-old male
- Reports often feeling fatigued, and struggles with domestic tasks
- Often experiences low-mood, unable to participate in and enjoy hobbies
- Has been experiencing GI symptoms and doesn't always want to take his medication in the hope of feeling 'normal' again

Findings from further investigations

- Liver-dominant NET of unknown primary origin
- SSTR positive
- Well-differentiated NET, intermediate grade Ki67 5–10%
- Positive for synaptophysin, chromogranin and serotonin; negative for trypsin, chymotrypsin, CEA, CK19 and glucagon
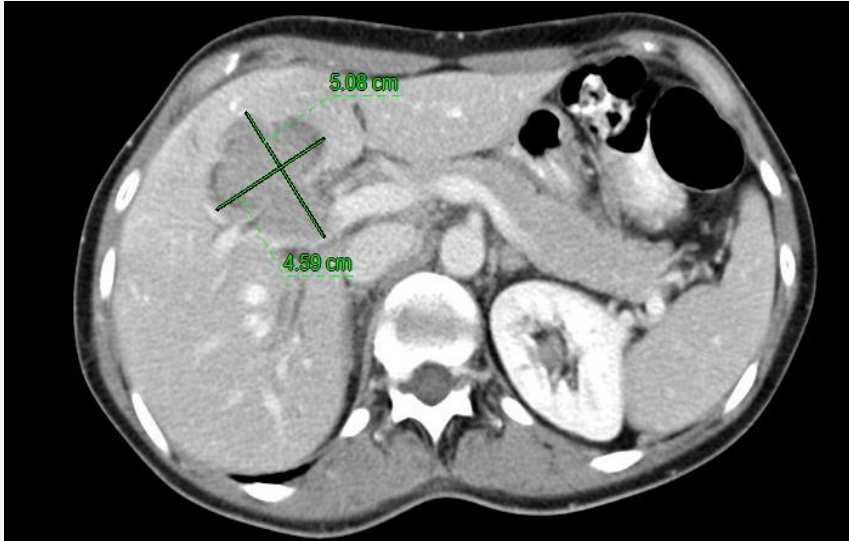
- Treatment: Resected, somatostatin analogue, hepatic embolization
- Starts to develop hormone-related symptoms at progression

CEA, carcinoembryonic antigen; CK19, cytokeratin 19; GI, gastrointestinal; NET, neuroendocrine tumour; SSTR, somatostatin receptor.

Clinical case 2: NET with liver-dominant disease

Original diagnostic imaging

15 years after original diagnosis

NET, neuroendocrine tumour.
Images provided courtesy of Dr Diane Reidy Lagunes.
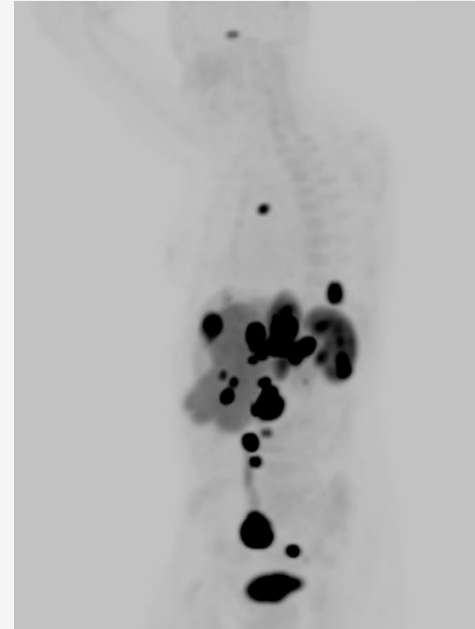
Clinical case 2 (liver-dominant disease): Trial data

Study	Population	Regimen	Key clinical outcomes
COMPETE[1,2] **Phase III RCT** (NCT03049189)	Inoperable, progressive SSTR-positive grade 1–2 GEP-NETs (N=309)	**[177]Lu-Edotreotide (DOTATOC)** vs everolimus	Primary endpoint: PFS *ACTIVE; NOT RECRUITING* Estimated completion date June 2029
^{177}Lu-DOTATOC[3,4] **Phase II retrospective**	Metastatic and progressive gastroenteric (50%), pancreatic (26.8%) and other primary site (23.2%) NETs (N=56; consecutively treated)	**[177]Lu-Edotreotide (DOTATOC)**	All NETs – survival outcomes mPFS, months (95% CI): **17.4** (7.9–26.9); **OS: 34.2** (17.2–51.3) mPFS: 32.0 months in patients with >1 cycle, compared to 3.8 months after a single cycle mPFS, months (95% CI) by NET type GEP-NET: **30.3** (9.3–51.3); **other: 6.0** (2.9–9.0) No SAEs observed AEs occurred in 61% patients – mostly GI and general disorders, or administration site-related

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Clinical case 3: Progressive pancreatic NET
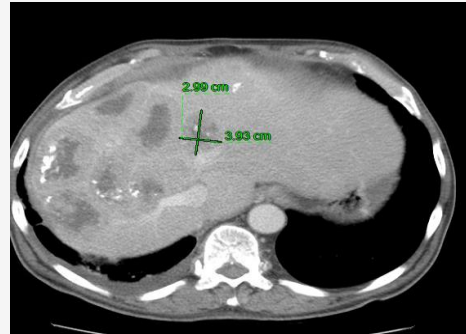
Presentation

- 62-year-old male previously diagnosed with a well-differentiated grade 2 pancreatic NET

- Currently receiving first-line therapy

- Recently has lost weight and often feels nauseous

- Has had regular abdominal pain in the last few weeks

Findings from further investigations

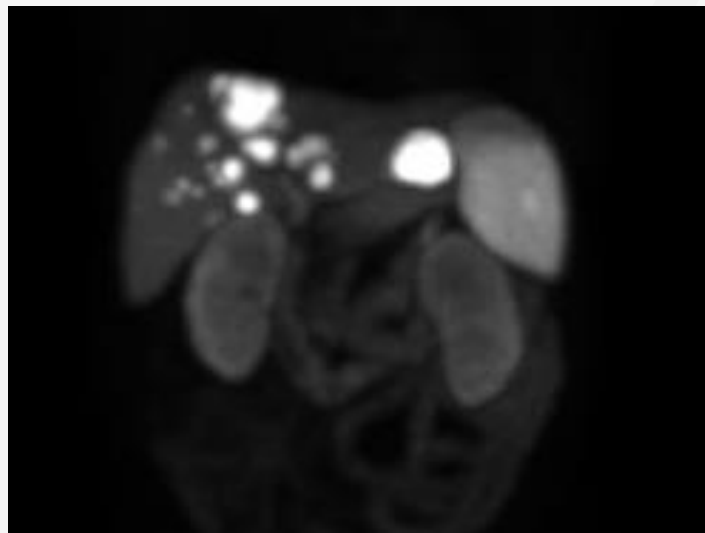Original diagnostic imaging

Imaging at follow-up after treatment

NET, neuroendocrine tumour.
Images provided courtesy of Dr Diane Reidy Lagunes.

Clinical case 3: Progressive pancreatic NET

Treatment break 3.5 years

- Progression with liver-predominant avid disease

Clinical case 3 (progressive pancreatic NET): Trial data

Study	Population	Regimen	Key clinical outcomes
COMPETE[1,2] **Phase III RCT** (NCT03049189)	**Inoperable, progressive SSTR-positive grade 1–2 GEP-NETs (N=309)**	**^{177}Lu-Edotreotide (DOTATOC)** vs everolimus	**Primary endpoint: PFS** *ACTIVE; NOT RECRUITING* Estimated completion date June 2029
COMPOSE[1] **Phase III RCT** (NCT04919226)	**Unresectable, well-differentiated SSTR-positive grade 2–3 GEP-NETs (N~202; consecutively treated)**	**^{177}Lu-Edotreotide (DOTATOC)** vs BSOC (everolimus or CAPTEM or FOLFOX)	**Primary endpoint: PFS** *RECRUITING* Estimated completion date September 2026
ECOG-ACRIN EA2211[1,3] **Phase II RCT** (NCT01824875)	**Advanced low/intermediate grade pancreatic NETs progressing within preceding 12 months No prior TEM, DTIC, CAP or 5FU (N=144)**	**TEM** vs CAPTEM	**At interim analysis (January 2018):** **mPFS, months: 14.4** vs **22.7; HR:** 0.58 **At final analysis (May 2021):** **mOS, months: 53.8** vs **58.7; HR:** 0.82 **RR: 34%** vs **40%** (p=0.59) **MGMT deficiency associated with greater OR for response** **Grade 3/4 AEs: 22%** vs **45%** (p=0.005)
SEQTOR[1] **Phase II RCT** (NCT02246127)	**Advanced grade 1–2 pancreatic NETs (N=141)**	Optimal sequencing of **everolimus/STZ-5FU** or **STZ-5FU/everolimus**	**Primary endpoint: First PFS at 12 months** Estimated completion date July 2021

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