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

Multidisciplinary panel

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Conversation 1

Achieving a timely and accurate diagnosis: How can multidisciplinary input address current challenges?

Dr Diane Reidy Lagunes
Medical Oncologist

Dr Thomas Hope
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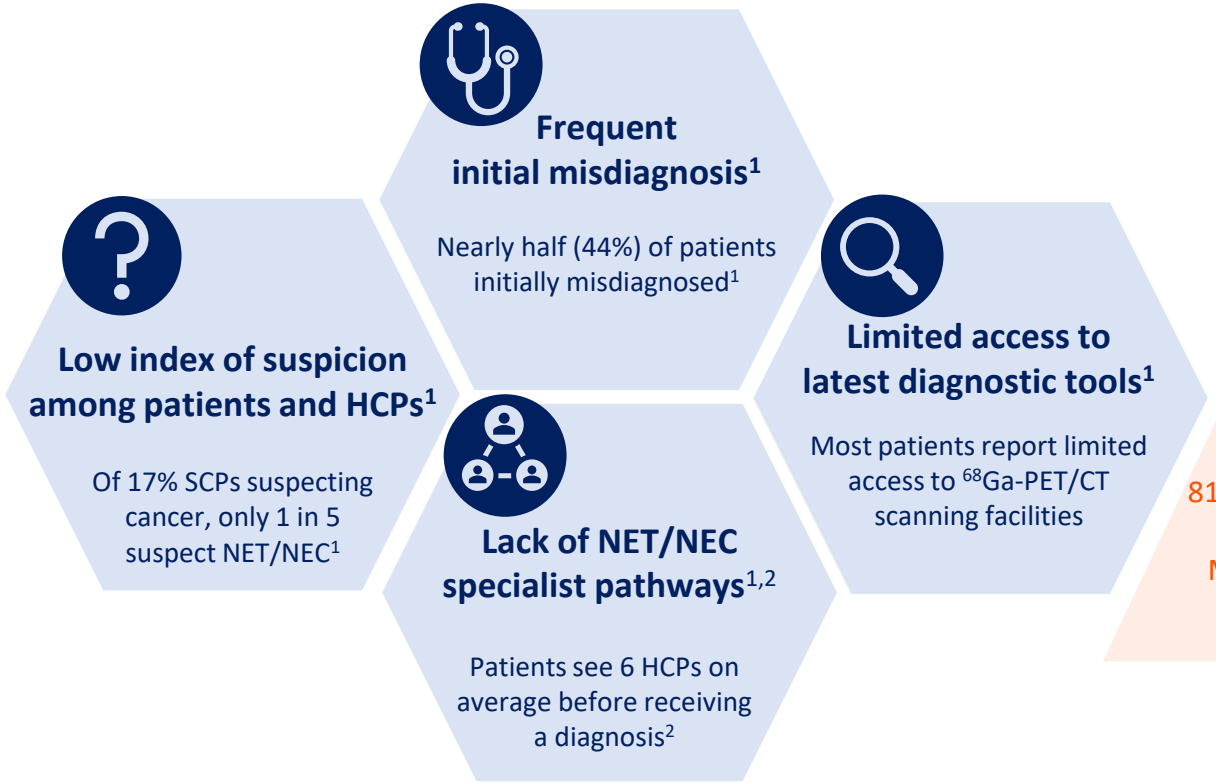
Achieving a NET/NEC diagnosis: Ongoing challenges



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%)

^{68}Ga-PET/CT, gallium-68 positron emission tomography/computerized tomography; HCP, healthcare professional; NEC, neuroendocrine carcinoma; NET, neuroendocrine tumour; SCP, secondary care physician.

1. Bouvier C, et al. *Curr Opin Endocrine Metabol Res.* 2021;18:254–7; 2. Singh S, et al. *J Glob Oncol.* 2017;3:43–53; 3. Kolarova T, et al. *Ann Oncol*. 2021;32(Suppl. 5):S917.

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Conversation 2

Mapping an individualized treatment plan:
What role does the multidisciplinary team play?

Dr Diane Reidy Lagunes
Medical Oncologist

Dr Thomas Hope
Nuclear Medicine Physician

Prof. Dr. med. Marianne Pavel
Endocrinologist

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

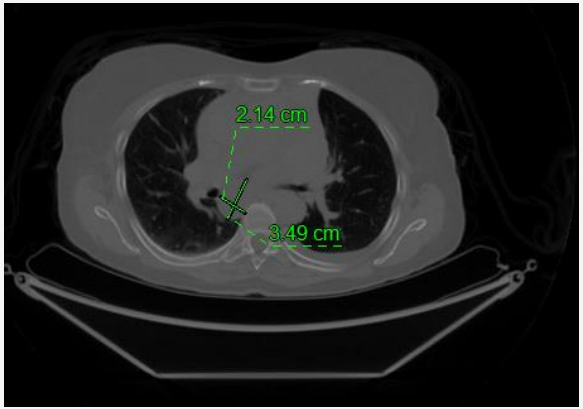
- Bronchopulmonary NET atypical carcinoid, Ki67 30%
- Positive for synaptophysin, chromogranin, CD56, INSM1, TTF-1, and Rb retained
- p53 wild-type expression

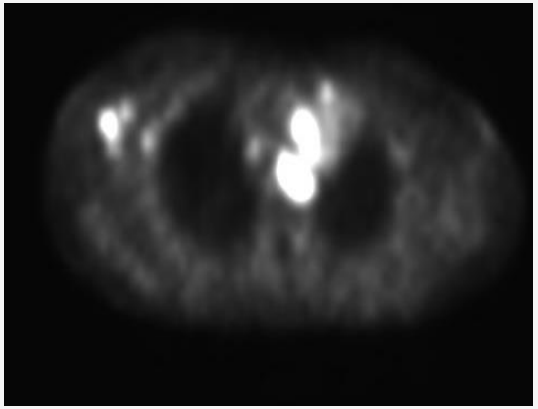
PET dotatate scan results:

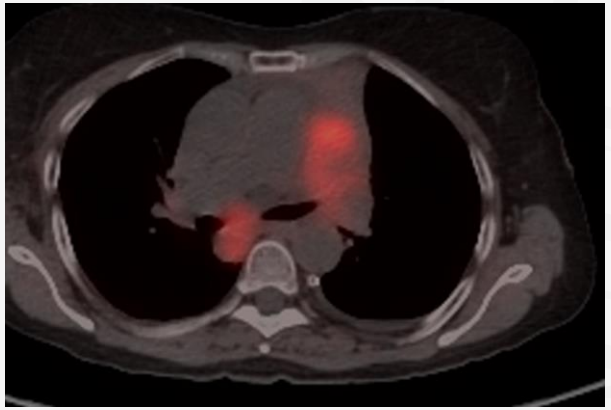
- Metastatic with tracer avid b/l SCLN (SUV 2.1), left perihilar/hilar (SUV 8.2), pleural lesions (SUV 7.5), moderate pleural effusion, left thoracic inlet 2.8x2.1 cm (SUV 8), left prevascular (SUV 8.1)
- Liver: No abnormal uptake
- Bones: Right base skull (SUV 3.3), right iliac wing SUV 2.1, right supra-acetabular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

Conversation 3

Supporting treatment adherence:
What strategies are needed for safety management?

Dr Diane Reidy Lagunes
Medical Oncologist

Dr Thomas Hope
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Ms Catherine Bouvier Ellis
NET Nursing Expert

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

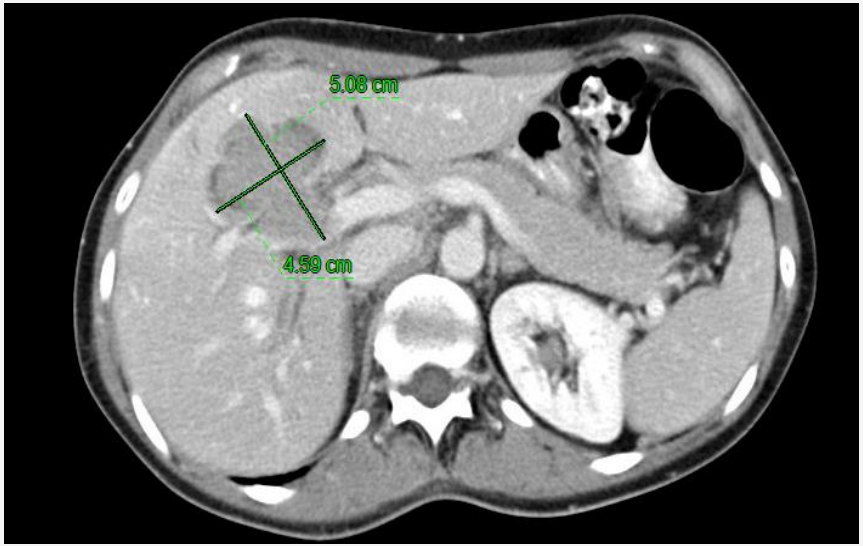
- Liver-dominant NET of unknown primary origin
- SSTR positive
- Well-differentiated NET, intermediate grade Ki67 5–10%
- Positive for synaptophysin, chromogranin and serotonin; negative for trypsin, chymotrypsin, CEA, CK19 and glucagon

- Treatment: Resected, somatostatin analogue, hepatic embolization
- Starts to develop hormone-related symptoms at progression

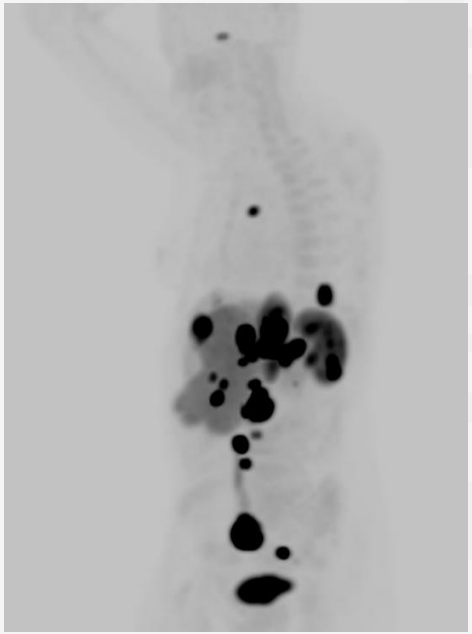
CEA, carcinoembryonic antigen; CK19, cytokeratin 19; GI, gastrointestinal; NET, neuroendocrine tumour; SSTR, somatostatin receptor.

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**

AE, adverse event; CI, confidence interval; GEP-NET, gastroenteropancreatic NET; NET, neuroendocrine tumour; OS, overall survival; mPFS, median progression-free survival; RCT, randomized controlled trial; SAE, serious AE; SSTR, somatostatin receptor.

1. ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/home (accessed 30 Aug 2022); 2. Wahba MM, et al. Cancer Res. 2021; 81(Suppl. 13):CT254; 3. Baum RP, et al. *J Clin Oncol.* 2016;34(Suppl. 4):436; 4. Baum RP, et al. *Theranostics.* 2016;6:501-10.

Conversation 4

Managing disease progression: Considerations for treatment selection and sequencing

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Prof. Dr. med. Marianne Pavel
Endocrinologist

Ms Catherine Bouvier Ellis
NET Nursing Expert

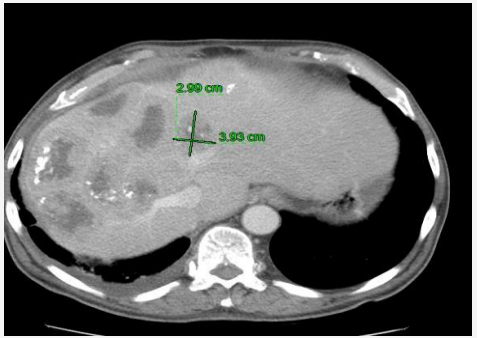
Clinical case 3: Progressive pancreatic NET

Presentation

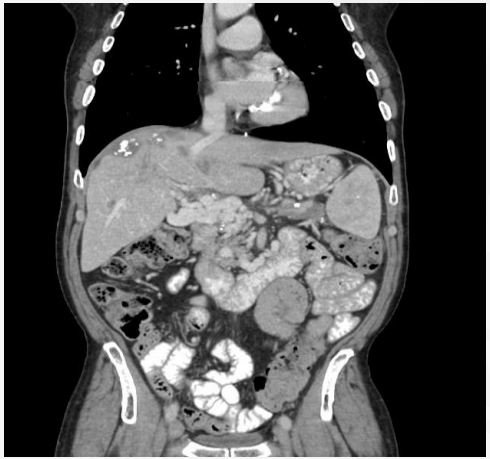
- 62-year-old male previously diagnosed with a well-differentiated grade 2 pancreatic NET
- Currently receiving first-line therapy
- Recently has lost weight and often feels nauseous
- Has had regular abdominal pain in the last few weeks

Findings from further investigations

Original diagnostic imaging



Imaging at follow-up after treatment



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

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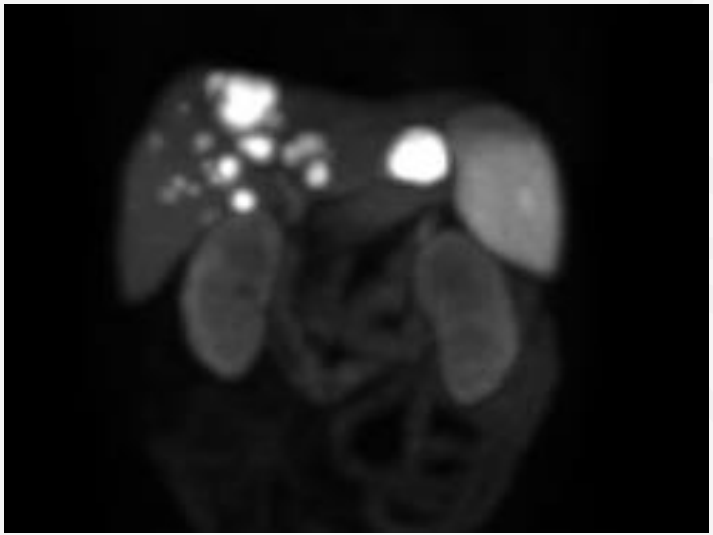
Clinical case 3: Progressive pancreatic NET

Treatment break 3.5 years

- Progression with liver-predominant avid disease



Images provided courtesy of Dr Diane Reidy Lagunes.

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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

5FU, 5-fluorouracil; AE, adverse event; BSOC, best standard of care; CAP, capecitabine; DTIC, dacarbazine; FOLFOX, folinic acid/fluorouracil/oxaliplatin; HR, hazard ratio; m, median; MGMT, O^6-methylguanine-DNA methyltransferase; NET, neuroendocrine tumour; OR, odds ratio; OS, overall survival; PFS, progression-free survival; RCT, randomized controlled trial; RR, response rate; SSTR, somatostatin receptor; STZ, streptozotocin; TEM, temozolomide.

1. ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/home (accessed 30 August 2022); 2. Wahba MM, et al. Cancer Res. 2021; 81(Suppl. 13):CT254; 3. Kunz P, et al. *J Clin Oncol.* 2022;40(Suppl. 16):4004.