OPTIMISING OUTCOMES IN GASTROINTESTINAL NEUROENDOCRINE TUMOURS

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NEUROENDOCRINE TUMOURS: OPTIMISING OUTCOMES

What are neuroendocrine tumours?
- Classification
- Symptoms

Multidisciplinary approach
- Investigations
- Treatment

The future
- Targeted molecular therapy
- Research
THE NEUROENDOCRINE SYSTEM

- **Neuro** = nerve
- **Endocrine** = network of glands and organs in the body that produce hormones
- Neuroendocrine cells found in endocrine glands – adrenal glands, pancreas, thyroid, pituitary and in ovaries and testes

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Neuroendocrine tumour (NET) = tumour of the neuroendocrine system
Most common locations are in the lungs and digestive system
“Carcinoid” – when tumours arise in the tubular gastrointestinal (GI) tract
Pancreatic neuroendocrine tumours (pNETs) when they arise in the pancreas
Gastrinomas when they arise in the proximal portion of the duodenum
The more accurate description is NET or gastroenteropancreatic (GEP) NET (two categories – tumours of luminal GI tract and pNETs)
NEUROENDOCRINE TUMOURS: HISTORY

- Mid-1800s – first identified
- 1907 – “Carcinoid” – a tumour that grew much more slowly than usual cancers
- 1950s – could spread from one part of the body to another like other forms of cancer
- 1952 – carcinoid heart disease identified
- 1953 – flushing effect of serotonin became clinically recognised

NEUROENDOCRINE TUMOURS: INCIDENCE

- Rare, incidence rising\(^1\) possibly due to increased detection of asymptomatic disease
- As diagnostic imaging increases in sensitivity, very small insignificant NETs may be coincidentally discovered
- Most are sporadic (causes unknown) but patients with multiple endocrine neoplasia (MEN), neurofibromatosis type 1 and von Hippel Lindau (VHL) are at increased risk

NEUROENDOCRINE TUMOURS: CLASSIFICATION

- NETs often grow slowly and it may take years before symptoms appear and tumour is diagnosed; well-differentiated

- Some NETs may be fast-growing; poorly-differentiated
## ENETS / WHO 2010

### Nomenclature and classification for digestive system NET

<table>
<thead>
<tr>
<th>Tumour differentiation</th>
<th>Grade</th>
<th>Mitotic count (in 10 high-power fields)</th>
<th>Ki-67 index (%)</th>
<th>ENETS / WHO classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well-differentiated</td>
<td>1 Low</td>
<td>&lt; 2</td>
<td>&lt; 3</td>
<td>Neuroendocrine tumour, Grade 1</td>
</tr>
<tr>
<td></td>
<td>2 Intermediate</td>
<td>2-20</td>
<td>3-20</td>
<td>Neuroendocrine tumour, Grade 2</td>
</tr>
<tr>
<td>Poorly-differentiated</td>
<td>3 High</td>
<td>&gt;20</td>
<td>&gt;20</td>
<td>Neuroendocrine carcinoma, Grade 3 (small cell)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Neuroendocrine carcinoma, Grade 3 (large cell)</td>
</tr>
</tbody>
</table>
NEUROENDOCRINE TUMOURS: NON-FUNCTIONING

- Non-functioning NETs:
  - Discovered incidentally during surgery or on an investigation being carried out for other reasons
  - Do not overproduce hormones
  - May not cause symptoms
NEUROENDOCRINE TUMOURS: SYMPTOMS

- Symptoms:
  - Pain
  - Nausea
  - Change in bowel habits
  - Lung – chest infections, shortness of breath, cough, haemoptysis

- Overproduction of hormones (functioning NETs):
  - Insulinomas – low blood glucose
  - Glucagonomas – high blood glucose
  - VIPomas – diarrhoea
  - Gastrinomas – ulcers
Some NETs (more commonly NETs of small bowel, large bowel or appendix) may overproduce serotonin

Serotonin causes a characteristic collection of symptoms called the carcinoid syndrome
# NEUROENDOCRINE TUMOURS: INVESTIGATIONS

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood tests</td>
<td>Routine blood tests - 5-HIAA (serum or urine), chromogranin A, gut hormones, NT proBNP, neuron-specific enolase</td>
</tr>
<tr>
<td>Imaging</td>
<td>- Computerised Tomography (CT) scan</td>
</tr>
<tr>
<td></td>
<td>- Magnetic Resonance Imaging (MRI)</td>
</tr>
<tr>
<td></td>
<td>- Functional imaging - Somatostatin receptor scintigraphy (111-In pentetreotide [Octreoscan] or Gallium Positron Emission Tomography (PET) scan)</td>
</tr>
<tr>
<td></td>
<td>- Echocardiogram</td>
</tr>
<tr>
<td>Biopsy</td>
<td>Establish differentiation</td>
</tr>
<tr>
<td>Endoscopy</td>
<td>Diagnosis, excision</td>
</tr>
<tr>
<td>Further tests</td>
<td>Bronchoscopy for lung NETs</td>
</tr>
</tbody>
</table>
SOMATOSTATIN RECEPTORS

- Somatostatin receptors 2 and 5 (SSTR2 and SSTR5) are expressed in 70-90% of NETs\(^1\)
- Result on somatostatin-receptor scintigraphy is one factor that predicts effectiveness of somatostatin analogue therapy
- Outcome according to SSTR expression not known

Pancreatic gastrinoma stained for the somatostatin receptor 2A; the cell membrane is stained brown (400x magnification)

Segment 1, 2, 3 and 4 of liver largely replaced and expanded by tumour

Infiltration of adjacent segments 5 and 8 with multiple smaller discrete tracer avid lesions in remaining segments

Multiple skeletal lesions demonstrating intense tracer uptake; T2 vertebra, right humeral head, left anterior second rib, sternum, sacrum, large destructive lesion left scapula
Because of the rarity of these tumours, not all doctors and local hospitals will have the full expertise to deal with this type of diagnosis.

Referral to a NET centre of excellence may be required.
NEUROENDOCRINE TUMOURS: MULTIDISCIPLINARY MEETING
NEUROENDOCRINE TUMOURS: TREATMENT

- Depends on:
  - Primary site of NET
  - Classification
  - Size of the tumour and whether it has metastasised
  - Whether patient has carcinoid syndrome or overproduction of other hormones
  - A watch and wait approach may be adopted in selected cases of incidental NETs
LOCALISED GASTROINTESTINAL NEUROENDOCRINE TUMOURS: TREATMENT

- Management by site:
  - Gastric
    - Management depends on type (whether 1, 2 or 3)
  - Pancreas
    - Resection indicated to alleviate symptoms due to hormone overproduction, local mass effect, prevent malignant transformation or dissemination
  - Ampulla of Vater
    - Resection
  - Small bowel NET
    - Resection
  - Appendix
    - <2 cm - simple appendicectomy (no mesoappendix invasion)
    - >2 cm or mesoappendiceal invasion – right hemicolecotomy
  - Rectal NET
    - <1 cm and T1 – local endoscopic resection
    - 1-2 cm – controversial – individualised treatment required
    - >2 cm – resection

1. Please refer to European Neuroendocrine Tumour Society (ENETS) guidelines 2016.
Follow-up:

May include:

- Biochemical markers (5-HIAA (serum or urine), chromogranin A, gut hormones, neuron-specific enolase)
- Imaging (as appropriate)
- Functional imaging (Somatostatin receptor scintigraphy (111-In pentetreotide [Octreoscan] or Gallium Positron Emission Tomography (PET) scan) should be performed where recurrence is suspected

1. Please refer to ENETS guidelines 2016.
There is no high level evidence to support the role of functional imaging (somatostatin receptor scintigraphy [111-In pentetreotide (Octreoscan)] or gallium positron emission tomography [PET] scan) in response evaluation of patients with advanced gastrointestinal NETs.
NEUROENDOCRINE TUMOURS: TREATMENT

- **Treatment goals:** (care tailored to suit individual patient)
  - Remove the tumour by surgery, however, if the tumour has metastasised, this may not be possible
  - Alleviate symptoms
  - Control tumour growth
  - Maintain patient quality of life
ADVANCED GASTROINTESTINAL NETS: INITIAL THERAPY

Hormone Hyper-secretion
- Somatostatin analogues
- Agents appropriate to specific syndrome

Resectable hepatic metastases
- Consider surgery

Asymptomatic
- Observation alone
- Somatostatin analogues at disease progression or if symptomatic
SOMATOSTATIN ANALOGUES

Placebo-Controlled, Double-Blind, Prospective, Randomized Study on the Effect of Octreotide LAR in the Control of Tumor Growth in Patients With Metastatic Neuroendocrine Midgut Tumors: A Report From the PROMID Study Group

Anja Rinke, Hans-Helge Müller, Carmen Schade-Brittinger, Klaus-Jochen Klose, Peter Barth, Matthias Wied, Christina Mayer, Behnaz Aminossadati, Ulrich-Frank Pape, Michael Bläker, Jan Harder, Christian Arnold, Thomas Gress, and Rudolf Arnold

Lanreotide in Metastatic Enteropancreatic Neuroendocrine Tumors

Martyn E. Caplin, D.M., Marianne Pavel, M.D., Jarosław B. Ćwikła, M.D., Ph.D., Alexandria T. Phan, M.D., Markus Raderer, M.D., Eva Sedláčková, M.D., Guillaume Cadot, M.D., Ph.D., Edward M. Wolin, M.D., Jaume Capdevila, M.D., Lucy Wall, M.D., Guido Rindi, M.D., Ph.D., Alison Langley, M.Sc., Séverine Martinez, B.Sc., Joëlle Blumberg, M.D., and Philippe Ruszniewski, M.D., Ph.D., for the CLARINET Investigators*

PROMID: OCTREOTIDE LAR - PHASE 3

- Patients with:
  - Treatment-naïve
  - Well differentiated (95% Ki-67 ≤2%)
  - Metastatic mid-gut NETs

- Primary endpoint:
  Time to tumour progression

Octreotide LAR significantly lengthens time to tumour progression compared with placebo in patients with functionally active and inactive metastatic midgut NETs.
CLARINET: LANREOTIDE - PHASE 3

- Tumours originated in pancreas, mid-gut, hindgut or of unknown origin
- 96% no tumour progression in 3-6 months before randomisation
- 84% patients had no previous treatment
- Well differentiated (Ki-67<10%)
- Primary endpoint: Progression-free survival (PFS)

Lanreotide is associated with significantly prolonged PFS among patients with metastatic enteropancreatic NETs (Grade 1 or 2)

CLARINET: LANREOTIDE – PHASE 3

PFS: According to sub-groups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Patients</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>204</td>
<td>0.47 (0.30–0.73)</td>
</tr>
<tr>
<td>Tumor origin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Midgut</td>
<td>73</td>
<td>0.35 (0.16–0.80)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>91</td>
<td>0.58 (0.32–1.04)</td>
</tr>
<tr>
<td>Hindgut</td>
<td>14</td>
<td>1.47 (0.16–13.24)</td>
</tr>
<tr>
<td>Other or unknown</td>
<td>26</td>
<td>0.21 (0.04–1.03)</td>
</tr>
<tr>
<td>Tumor grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>141</td>
<td>0.43 (0.25–0.74)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>61</td>
<td>0.45 (0.22–0.91)</td>
</tr>
<tr>
<td>Hepatic tumor volume</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤25%</td>
<td>137</td>
<td>0.34 (0.18–0.62)</td>
</tr>
<tr>
<td>&gt;25%</td>
<td>67</td>
<td>0.45 (0.23–0.88)</td>
</tr>
</tbody>
</table>

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CLARINET¹: LANREOTIDE - PHASE 3 (pNET)

**PFS:** According to pNET² sub-group

- Mean age – 64 years both groups
- Overall: 37% had hepatic tumour load >25%, 95% stable disease, 77% had received no previous treatment, 38% had previous surgery on the tumour
- No new safety concerns
- The positive risk-benefit profile for lanreotide depot in pNETs is consistent with overall findings in CLARINET

**Median progression-free survival data²**

**Lanreotide:** not reached

**Placebo:** 12.1 months
(95% CI 9.4-18.3 months)

HR for progressive disease/death 0.58, 95% CI 0.32-1.04

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PANCREATIC NETS: PROGRESSIVE DISEASE

Progressive disease
- Symptomatic
  - Somatostatin analogues
  - Everolimus
  - Sunitinib

Symptomatic from tumour bulk
  - Somatostatin analogues +/- targeted therapy

Highly symptomatic
  - Chemotherapy¹

Liver-predominant disease
  - Hepatic arterial embolisation

**EVEROLIMUS (RADIANT-3)¹**: pNET PHASE 3

- **Everolimus**: Oral inhibitor of mammalian target of rapamycin (mTOR)
- Patients with:
  - Advanced, low- or intermediate-grade pNET
  - 40% therapy naïve
  - Radiologic progression within previous 12 months
- Primary endpoint: Progression-free survival

![Graph showing progression-free survival rates for Everolimus and Placebo](image)

Kaplan-Meier median:
- Everolimus, 11.4 mo
- Placebo, 5.4 mo

Hazard ratio: 0.34 (95% CI, 0.26–0.44)
P<0.001 by one-sided log-rank test

**Mature median overall survival data²**

**Everolimus**: 44.02 months
(95% CI 35.61-51.75)

**Placebo**: 37.68 months
(95% CI 29.14-45.77)

- HR 0.94, 95% CI 0.73-1.20, P=0.30

Crossover of majority of patients (85%) may have confounded results.

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SUNITINIB: pNET PHASE 3

- Sunitinib: Multi-targeted tyrosine kinase inhibitor
- Patients with:
  - Well-differentiated advanced pNETs
  - Majority had received prior systemic therapy
  - Radiologic progression within previous 12 months
- Primary endpoint: Progression-free survival

SUNITINIB:
- pNET PHASE 3
- Double blind
- Placebo (n=85)
- Sunitinib (n=86)
- 37.5mg/day continuously

Sunitinib improved PFS and OS as compared to placebo in patients with advanced pNETs.

SMALL BOWEL NETS: PROGRESSIVE DISEASE

Symptomatic from tumour bulk → Somatostatin analogues +/- Chemotherapy

Liver-predominant disease → Hepatic arterial embolisation

Refractory to medical therapy → Peptide receptor radioligand therapy (PRRT) – where available
PEPTIDE RECEPTOR RADIONUCLIDE THERAPY: PRRT

- Use of targeted radiotherapy using radiolabeled somatostatin analogues, in the treatment of patients with NETs
- Data previously generated in populations of patients with combined pancreatic and gastrointestinal NETs
- In general, objective tumour response rates were up to 30%
- Approximately one-third of patients had symptomatic improvement\(^1\)

Evaluate the efficacy and safety of $^{177}$Lu-Dotatate plus Octreotide 30 mg compared to Octreotide LAR 60 mg (off-label use) in patients with inoperable, somatostatin receptor positive, midgut NET, progressive on Octreotide LAR 30 mg.

**AIM**

International, multicentre, randomised, comparator-controlled, parallel-group

**DESIGN**

**Treatment and Assessments**

Tumour burden assessment (RECIST criteria) every 12 weeks

**BASELINE AND RANDOMISATION**

- $n = 115$
- 4 administrations of 7.4 GBq of $^{177}$Lu-Dotatate every 8 weeks + Octreotide 30 mg
- $n = 115$
- Octreotide LAR 60mg every 4 weeks

5 Years follow up

2. FDA and EMA recommendation.
NETTER-1: PROGRESSION-FREE SURVIVAL

N = 229 (ITT)
Number of events: 90

- $^{177}$Lu-Dotatate: 23
- Oct 60 mg LAR: 67

HR [95% CI]
0.209 [0.129 – 0.338]
p < 0.0001

Significant increase in PFS in patients with advanced midgut NETs treated with $^{177}$Lu-Dotatate

Patients with well-differentiated (G1/G2), advanced, progressive, nonfunctional NET of lung or GI origin (N=302).
- Absence of active or any history of carcinoid syndrome.
- Pathologically-confirmed advanced disease.
- Radiologic disease progression in ≤ 6 months.

Endpoints:
- **Primary:** PFS (central)
- **Key Secondary:** OS
- **Secondary:** ORR, DCR, safety, HRQoL (FACT-G), WHO PS, NSE/CgA, PK

Stratified by:
- Prior SSA treatment (yes vs. no)
- Tumour origin (stratum A vs. B)*
- WHO PS (0 vs. 1)

*Based on prognostic level, grouped as: **Stratum A (better prognosis)** — appendix, caecum, jejunum, ileum, duodenum, and NET of unknown primary. **Stratum B (worst prognosis)** — lung, stomach, rectum, and colon except caecum.
Crossover to open-label everolimus after progression in the placebo arm was not allowed prior to the primary analysis.

52% reduction in the relative risk of progression or death with everolimus vs placebo

HR = 0.48 (95% CI, 0.35-0.67); P < 0.00001

Kaplan–Meier medians

**Everolimus:** 11.0 months (95% CI, 9.23-13.31)

**Placebo:** 3.9 months (95% CI, 3.58-7.43)

*Censoring Times*

**Everolimus** (n/N = 113/205)

**Placebo** (n/N = 65/97)

No. of patients still at risk

<table>
<thead>
<tr>
<th></th>
<th>Everolimus</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Month</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>205</td>
<td>97</td>
</tr>
<tr>
<td>2</td>
<td>168</td>
<td>65</td>
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<tr>
<td>4</td>
<td>145</td>
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</tr>
<tr>
<td>24</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*P*-value is obtained from the stratified one-sided log-rank test; Hazard ratio is obtained from stratified Cox model.

Telotristat etiprate is a novel inhibitor of tryptophan hydroxylase, the rate-limiting enzyme in serotonin biosynthesis.


**TELESTAR: STUDY DESIGN**

- **3- to 4-week run-in (n=135)**
  - Run in: Evaluation of bowel movement (BM) frequency (well differentiated metastatic NET with documented carcinoid syndrome with ≥4 BMs/day).

- **1:1:1**
  - Placebo TID (n=45)
  - Telotristat etiprate 250 mg TID (n=45)
  - Telotristat etiprate 500 mg TID* (n=45)

- **Evaluation of primary endpoint:**
  - Reduction in number of daily BMs from baseline (averaged over 12-week double-blind treatment phase)

All patients required to be on SSA at enrollment and continue SSA therapy throughout study period.

*Including a blinded titration step of one week of 250 mg TID.

BM; bowel movement, SSA; somatostatin analogue, TID; three times daily.


Hodges–Lehmann estimator of treatment differences showed a median reduction versus placebo of
–0.81 BMs daily for telotristat etiprate 250 mg dose \( (P<0.001) \)
–0.69 for telotristat etiprate 500 mg dose \( (P<0.001) \)

Systemic chemotherapy with a platinum-based combination regimen, analogous to that used for small cell lung cancer

- Anti-tumoural activity and high tumour response rates (41-67%) \(^1\)
- No established second-line treatment
- All studies to date are small retrospective series:
  - FOLFIRI\(^2\) (N=19)
  - FOLFOX\(^3\) (N=21)
  - Temozolomide-based regimens\(^4\) (N=25)
  - Topotecan\(^5\) (N=22)
  - Taxotere-based chemotherapy\(^6\) (N=20)
THE FUTURE

Some ongoing studies\(^1\):

- **Maintenance therapy**
  - Lanreotide as maintenance therapy in patients with non-resectable duodeno-pancreatic NETs (REMINET – NCT 02288377)

- **Sequencing of therapy**
  - Everolimus followed by Streptozotocin/5-fluorouracil upon progression or reverse sequence in pancreatic NET (SEQTOR – NCT 02246127)

- **Combination therapy with PRRT and chemotherapy**
  - Capecitabine/Temozolomide +/- PRRT in patients with well-differentiated midgut NETs (NCT 02358356)
THANK YOU