NET CONNECT
EXPERTS KNOWLEDGE SHARE
with
Prof Marianne Pavel
Dr Jaume Capdevila
Dr Louis de Mestier
Dr Angela Lamarca

TREATMENT SEQUENCING IN ADVANCED DIGESTIVE NET

Barcelona, Spain
Saturday 28th September
20:30–22:00
DISCLOSURE

NET CONNECT

is supported by an Independent Educational Grant from IPSEN

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NET CONNECT
EXPERTS KNOWLEDGE SHARE 2019

THE SCIENTIFIC COMMITTEE

• Prof. Marianne Pavel
• Dr. Jaume Capdevila
• Dr. Angela Lamarca
• Dr. Louis de Mestier

THE DISCUSSION

Treatment sequencing in advanced digestive NET: Challenges in clinical practice

BACKGROUND AND APPROACHES CONSIDERED

• Overview of available treatment options and key trials - Dr. Capdevila
• Treatment choices for Metastatic low grade SI-NET- Dr. de Mestier
• Treatment choices for Metastatic grade 2 pNET- Dr. Lamarca
• Summary of discussion – Prof. Pavel
SCIENTIFIC COMMITTEE DISCLOSURES

• Prof Marianne Pavel has received financial research support from IPSEN and Novartis (former institution), and consultation or speaker fees from the following companies: IPSEN, Novartis, Pfizer, Lexicon, Prime Oncology

• Dr Jaume Capdevila has received financial support/sponsorship for research support, consultation or speaker fees from the following companies: Bayer, Eisai, Advanced Accelerator Applications, Novartis, IPSEN, Pfizer, Merck, Sanofi, Amgen

• Dr Louis de Mestier has received financial support/sponsorship for research support, consultation or speaker fees from the following companies: IPSEN, Novartis, Pfizer

• Dr Angela Lamarca has received honoraria or consultation fees: Eisai, Nutricia, IPSEN; Participation in company sponsored speaker bureau: Pfizer, IPSEN, Merck, Incyte; Travel, education funding: IPSEN, Pfizer, Bayer, AAA, Sirtex, Novartis, Mylan, Delcath
OVERVIEW

Dr Jaume Capdevila, MD, PhD
Gastrointestinal and Endocrine Tumours Group, Vall d’Hebron University Hospital and Vall d’Hebron Institute of Oncology (VHIO), Barcelona, Spain
CDK4/6, Cyclin-dependent kinase 4/6; CS, carcinoid syndrome; GEP-NET, gastroenteropancreatic neuroendocrine tumours; GI NET, gastrointestinal neuroendocrine tumour; HDAC, histone deacetylase; IFN, interferon; pNET, pancreatic neuroendocrine tumour; PRRT, peptide receptor radionuclide therapy; RFA, radiofrequency ablation; SIRT, selective internal radiation therapy; STZ/5-FU, streptozotocin/fluorouracil; TACE, transarterial chemoembolization; TAE, transarterial embolization; TKI, tyrosine kinase inhibitors; TMZ, Temozolomide. Slide provided by Prof. Marianne Pavel
NOVEL AGENTS FOR NEUROENDOCRINE TUMOURS

• In the past 10 years, a number of key trials reported resulting in the availability of new treatments for NETs:
  – **PROMID**: Octreotide
  – **RADIANT-3 & RADIANT-4**: Everolimus
  – **CLARINET**: Lanreotide
  – **NETTER-1**: $^{177}$Lu-DOTATATE
  – **TELESTAR/ TELECAST**: Telotristat Ethyl
  – **Study A6181111**: Sunitinib
  – **ECOG-ACRIN study E2211**: Temozolomide

• These trials have contributed to the current treatment recommendations and therapeutic algorithm.

PROMID STUDY

OCTREOTIDE VS PLACEBO IN MIDGUT-NET

PRIMARY ENDPOINT: TTP

SECONDARY ENDPOINT: OS

CI, confidence interval; HR, hazard ratio; LAR, long acting release; OS; overall survival; SI-NET, small intestine neuroendocrine tumour; TTP, time to tumour progression.

RADIANT-3 STUDY
EVEROLIMUS VS PLACEBO IN PAN-NET

PRIMARY ENDPOINT: PFS

N = 410
Everolimus: 207
Placebo: 203

Kaplan–Meier median
Everolimus, 11.0 mo
Placebo, 4.6 mo
Hazard ratio, 0.35 (95% CI, 0.27–0.45)
P<0.001 by one-sided log-rank test

SECONDARY ENDPOINT: OS

Kaplan–Meier median
Everolimus, NA
Placebo, NA
Hazard ratio, 1.05 (95% CI, 0.71–1.55)
P=0.59 by one-sided log-rank test

CI, confidence interval; mo, months; NA, not available; OS, overall survival; PFS, progression-free survival.
RADIANT-4 STUDY

EVEROLIMUS VS PLACEBO IN LUNG, INTESTINAL NET AND NET OF UNKNOWN ORIGIN

PRIMARY ENDPOINT: PFS

SECONDARY ENDPOINT: OS (premature)

Kaplan-Meier median progression-free survival
Everolimus 11.0 months (95% CI 9.2–13.3)
Placebo 3.9 months (95% CI 3.6–7.4)
HR 0.48 (95% CI 0.35–0.67)
p<0.00001 by stratified one-sided log-rank test

Kaplan-Meier median overall survival
Everolimus 19.8 months (95% CI 15.7–24.9)
Placebo 8.1 months (95% CI 7.4–8.4)
HR 0.64 (95% CI 0.40–1.05)
p=0.037 by stratified one-sided log-rank test

OS accordingly to interim analysis.
CI, confidence interval; HR, hazard ratio; NA, not available; OS, overall survival, PFS, progression-free survival.
CLARINET STUDY
LANREOTIDE VS PLACEBO IN GEP-NET

PRIMARY ENDPOINT: PFS

SECONDARY ENDPOINT: OS (premature)

PFS accordingly to central investigation
CI, confidence interval; GEP-NET, gastroenteropancreatic neuroendocrine tumour; OS, overall survival; PFS, progression-free survival.
NETTER-1 STUDY

177LU-DOTATATE VS HIGH DOSE OCTREOTIDE IN MIDGUT NET

PRIMARY ENDPOINT: PFS

SECONDARY ENDPOINT: OS (premature)

Primary analysis of NETTER-1 with interim analysis of overall survival. CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; mPFS, median progression free survival; NR, not reached; LAR, long acting release; Lu, lutetium; Oct, octreotide, OS, overall survival.

TELESTAR STUDY

TELOTRIXSTAT ETHYL VS PLACEBO

SYMPTOM CONTROL IN REFRACTORY CARCINOID SYNDROME (PHASE 3)

44 and 42% patients treated with Telotristat (250 mg and 500 mg respectively) had a durable benefit

(≥30% Reduction of diarrhea for ≥50% of the double-blind study period)

STUDY A6181111

SUNITINIB VS PLACEBO IN PANCREATIC NET

PRIMARY ENDPOINT: PFS

Hazard ratio, 0.42 (95% CI: 0.26 – 0.66)  
P<0.001

SECONDARY ENDPOINT: OS

Hazard ratio, 0.41 (95% CI: 0.19 – 0.89)  
P=0.02

CI, confidence interval; PFS, progression free survival; OS, overall survival.
ECOG-ACRIN STUDY (E2211)

TEMZOLOMIDE VS TEMZOLOMIDE + CAPECITABINE IN PANCREATIC NET

**PRIMARY ENDPOINT: PFS**

- TEM 14.4 mo
- TEM+CAP 22.7 mo

**SECONDARY ENDPOINT: OS**

- TEM 38.0 mo
- TEM+CAP NR

CAP, capecitabine; CI, confidence interval; NR, not reached; OS, overall survival.; PFS, progression free survival; TEM, temozolomide

Kunz, PL et al. ASCO 2018 Abstract #4004
**Therapeutic options and conditions for preferential use as first-line therapy in advanced NEN**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Functionality</th>
<th>Grading</th>
<th>Primary site</th>
<th>SSTR status</th>
<th>Special considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Octreotide</td>
<td>+/-</td>
<td>Gl</td>
<td>Midgut</td>
<td>+</td>
<td>Lower tumor burden</td>
</tr>
<tr>
<td>Lanreotide</td>
<td>+/-</td>
<td>G1/G2 (~10%)</td>
<td>Midgut, pancreas</td>
<td>+</td>
<td>Low and high (&gt;25%) liver tumor burden</td>
</tr>
<tr>
<td>IFN-alpha 2b</td>
<td>+/-</td>
<td>G1/G2</td>
<td>Midgut</td>
<td></td>
<td>If SSTR negative</td>
</tr>
<tr>
<td>STZ/S-FU</td>
<td>+/-</td>
<td>G1/G2</td>
<td>Pancreas</td>
<td></td>
<td>Progressive in short-term* or high tumor burden or symptomatic</td>
</tr>
<tr>
<td>TEM/CAP</td>
<td>+/-</td>
<td>G2</td>
<td>Pancreas</td>
<td></td>
<td>Progressive in short-term* or high tumor burden or symptomatic; if STZ is contraindicated or not available</td>
</tr>
<tr>
<td>Everolimus</td>
<td>+/-</td>
<td>G1/G2</td>
<td>Lung</td>
<td></td>
<td>Atypical carcinoid and/or SSTR negative</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pancreas</td>
<td></td>
<td>Insulinoma or contraindication for CTX</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Midgut</td>
<td>+</td>
<td>If SSTR negative</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>+/-</td>
<td>G1/G2</td>
<td>Pancreas</td>
<td></td>
<td>Contraindication for CTX</td>
</tr>
<tr>
<td>PRRT</td>
<td>+/-</td>
<td>G1/G2</td>
<td>Midgut</td>
<td>+ (required)</td>
<td>Extended disease; extrahepatic disease, e.g. bone metastasis</td>
</tr>
<tr>
<td>Cisplatin§/etoposide</td>
<td>+/-</td>
<td>G3</td>
<td>Any</td>
<td></td>
<td>All poorly differentiated NEC</td>
</tr>
</tbody>
</table>

* ≤6–12 months; §Cisplatin can be replaced by carboplatin.
# Overview of Key On-going Clinical Trials in NETs

## Pancreatic NETs
- **2018**
  - **E2201** Spartalizumab
- **2019**
  - **SUNEVO** Sunitinib + Evofosamide
- **2020**
  - **DUNE** Durvalumab + Tremelimumab
- **2021**
  - **SEQTOR** Everolimus vs STZ-SFU
  - **COMPETE** Everolimus vs 177Lu-edotreotide
- **2022**
  - **CABATEN** Cabozantinib + Atezolizumab

## Non-Pancreatic NETs
- **2019**
  - **SANET-p** Surufatinib vs Placebo
- **2020**
  - **AXINET** Axitinib + Octreotide vs Octreotide
  - **DUNE** Durvalumab + Tremelimumab
- **2021**
  - **COMPETE** Everolimus vs 177Lu-edotreotide
- **2022**
  - **CABINET** Cabozantinib vs Placebo

## NECs
- **2018**
  - **E2201** Spartalizumab
- **2021**
  - **NABNEC** NAB-Paclitaxel + Carboplatin vs Carboplatin-Etoposide
  - **DUNE** Durvalumab + Tremelimumab
  - **EVINEC** Everolimus

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*Presented by Dr. Enrique Grande, ESMO 2019*
DOES ONE SIZE FIT ALL?
The following patient case studies will help answer this question.
PATIENT CASE 1: METASTATIC LOW G2 (ki67 5%) SMALL INTESTINE NET

Dr Louis de Mestier, MD
Dept Gastroenterology-Pancreatology
ENETS Centre of Excellence
Beaujon Hospital, University of Paris
Clichy, France
THERAPEUTIC OPTIONS FOR ADVANCED SI NET

- Watch and wait
- Long-acting somatostatin analogs
- Resection ablation of metastases
- Liver transarterial embolization
- $^{177}\text{Lu}$-DOTATATE PRRT
- Everolimus
- Interferon-alpha
- Chemotherapy
- Clinical trials

There is no unique adequate sequence
Treatment must be individualized

Lu, Lutetium; SI NET, small intestine neuroendocrine tumour; PRRT, peptide receptor radionuclide therapy.
**Therapeutic Decision Must Be Personalized**

Management of Intestinal (Midgut) NEN

| CS, Carcinoid Syndrome; FOLFIRI, Folinic Acid, Fluorouracil and Irinotecan; FOLFOX, Folinic Acid, Fluorouracil and Oxaliplatin; IFN, Interferon; LM, Liver Metastasis; NEC, Neuroendocrine Carcinoma; NEN, Neuroendocrine Neoplasm; PD, Progressive Disease; PRRT, Peptide Receptor Radi nuclide Therapy; SD, Stable Disease; SSA, Somatostatin Analogues; SSTR, Somatostatin Receptor; TEM/CAP, Temozolomide-Capecitabine. Pavel, et al. Neuroendocrinology. 2016;103:172-85. |
CASE 1: MR. D. O.

• 42 years old
• No particular history
• June 2014: abdominal pain and postprandial flushing. WHO-PS = 0
• CT-scan and MRI: multiple liver mets, mesenteric lymph-node complex
• Liver biopsy: well-diff NET, Ki67 = 5%
• Positive SST-receptor scintigraphy
• 5-HIAA = 4xN, Echocardiography: no sign of carcinoid heart disease

5-HIAA, 5-hydroxyindoleacetic acid; CT, computed tomography; MRI, magnetic resonance imaging; NET, neuroendocrine tumour; SST, somatostatin; WHO-PS, world health organisation performance status.
WHAT TREATMENT SHOULD WE CONSIDER FIRST?

• SST analogs with antisecretory intent?

• Surgery of the primary tumour(s) and associated LN metastases?

• Treatment of the metastatic disease:
  – Watch and wait?
  – SST analogs?
  – Liver transarterial embolization?
  – Everolimus?
  – $^{177}$Lu-DOTATATE PRRT?
  – Chemotherapy?

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LN, lymph node; Lu, Lutetium; NET, neuroendocrine tumour; PRRT, peptide receptor radionuclide therapy; SST, somatostatin.
WHAT TREATMENT SHOULD WE CONSIDER FIRST?

• SST analogs with antisecretory intent
• Surgery of the primary tumour(s) and associated LN metastases
• Treatment of the metastatic disease:
  – Watch and wait?
  – SST analogs
  – Liver transarterial embolization?
  – Everolimus?
  – $^{177}$Lu-DOTATATE PRRT?
  – Chemotherapy?

LN, lymph node; Lu, Lutetium; PRRT, peptide receptor radionuclide therapy; SST, somatostatin.
WHAT TREATMENT SHOULD WE CONSIDER FIRST?

• July 2014:
  – Right ileocolectomy, mesenteric lymphadenectomy, cholecystectomy
  – 6 siNETs, max 2 cm, pT4N+M+, Ki67 = 5%

• July 2014: lanreotide AG 120 mg

• December 2015: carcinoid syndrome not completely controlled

• CT: Hepatic progression, increase in size and new lesions, no new lesions elsewhere

AG, autogel; CT, computed tomography; siNETs, small intestine neuroendocrine tumour.
WHAT SECOND-LINE TREATMENT?

- Double-dose SST analogs?
- Liver transarterial embolization?
- Everolimus?
- $^{177}\text{Lu-DOTATATE PRRT}$?
- Chemotherapy?

- G2, liver involvement 30-50 %
- Fast progression under SST analogs
- Uncontrolled functioning syndrome
- Disease restricted to the liver
- Positive SST-receptor imaging

Lu, Lutetium; PRRT, peptide receptor radionuclide therapy; SST, somatostatin.
WHAT SECOND-LINE TREATMENT?

• Double-dose SST analogs?
• Liver transarterial embolization
• Everolimus?
• $^{177}$Lu-DOTATATE PRRT?
• Chemotherapy?

• G2, liver involvement 30-50 %
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• Disease restricted to the liver
• Positive SST-receptor imaging

Lu, Lutetium; PRRT, peptide receptor radionuclide therapy; SST, somatostatin.
WHAT SECOND-LINE TREATMENT?

- January 2016 and April 2016:
  - 2 procedures of liver transarterial embolization + continuation of lanreotide AG 120 mg / 28 days
  - Good symptomatic response
  - Prolonged morphological control

December 2015  July 2016  July 2017
WHAT HAPPENED NEXT

• The patient remained stable until April 2018
• Mild carcinoid syndrome under SST analogue
• Recent weight loss and abdominal pain, flushing (3 per day) and diarrhea (5 BM per day)
• 5-HIAA 8N and CgA 10N
• CT, MRI and DOTATOC-PET: liver and extrahepatic progression

5-HIAA, 5-hydroxyindoleacetic acid; BM, bowel movements; CgA, chromogranin A; CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography; SST, somatostatin.
WHAT THIRD-LINE TREATMENT ?

- Liver transarterial embolization ?
- Everolimus ?
- $^{177}$Lu-DOTATATE PRRT ?
- Chemotherapy ?

Lu, Lutetium; PRRT, peptide receptor radionuclide therapy; SST, somatostatin.
WHAT THIRD-LINE TREATMENT?

- Liver transarterial embolization?
- Everolimus?
- $^{177}$Lu-DOTATATE PRRT
- Chemotherapy?

- G2, liver involvement 30-50 %
- Progression
- Uncontrolled functioning syndrome
- Extra-hepatic disease
- Positive SST-receptor imaging

Lu, Lutetium; PRRT, peptide receptor radionuclide therapy; SST, somatostatin.
WHAT THIRD-LINE TREATMENT?

- May 2018 to January 2019: 4 cycles of 177Lu-DOTATATE, yielded tumour control
- April 2019: clinical worsening: WHO-PS 1-2, weight loss, abdominal pain, carcinoid syndrome
- MRI: progression, increase in size and new lesions (liver and lymph nodes)

Lu, lutetium; MRI, magnetic resonance imaging; WHO-PS, world health organisation performance status.
WHAT FOURTH-LINE TREATMENT?

- Liver transarterial embolization?
- Everolimus?
- Chemotherapy?
- Best supportive care?

- G2, liver involvement 50%  
- Fast progression  
- Uncontrolled functioning syndrome  
- Extra-hepatic disease  
- Signs of liver deterioration
WHAT FOURTH-LINE TREATMENT?

- Liver transarterial embolization?
- Everolimus?
- Chemotherapy
- Best supportive care?

- G2, liver involvement 50%
- Fast progression
- Uncontrolled functioning syndrome
- Extra-hepatic disease
- Signs of liver deterioration
WHAT FOURTH-LINE TREATMENT?

- May 2019 to September 2019: 5 cycles of FOLFOX-bevacizumab
- Clinical worsening: WHO-PS 3, abdominal pain, carcinoid syndrome
- CT-scan: progression
- Decision of palliative care

CT, computed tomography; FOLFOX, folinic acid, fluorouracil and oxaliplatin; WHO-PS, world health organisation performance status.
SUMMARY – CASE 1

Chemo, chemotherapy; CS, carcinoid syndrome; FOLFIRI, folinic acid, fluorouracil and irinotecan; FOLFOX, folinic acid, fluorouracil and oxaliplatin; IFN, interferon; LM, liver metastasis; NEC, neuroendocrine carcinoma; PD, progressive disease; PRRT, peptide receptor radionuclide therapy; SD, stable disease; SSA, somatostatin analogues; SST, somatostatin; SSTR, somatostatin receptor; TEM/CAP, temozolomide-capecitabine.

Dose escalation of SSA is still a considerable approach, particularly if not only diarrhea is present but also flushing symptoms. Pasireotide can be considered (off-label) if all other options failed.
PATIENT CASE 2:
METASTATIC GRADE 2 Pan-NET, ki67 15%

Dr Angela Lamarca MD, PhD, MSc
Department of Medical Oncology
The Christie NHS Foundation Trust
University of Manchester
United Kingdom
POTENTIAL OPTIONS OF TREATMENT FOR Pan-NETs

1. Chemotherapy (TemCap; STZ/5-FU)
2. Clinical trials
3. Everolimus
4. IFN-alpha
5. Liver-directed therapies
6. PRRT
7. SSA
8. Sunitinib
9. Surgery
10. Watch and wait

Could you order them by preference to be used in patients with Pan-NETs?

If all patients received all options of therapy: 3,628,800 possible sequences

Is there only 1 correct answer?

IFN, interferon; Pan-NETs, pancreatic neuroendocrine tumours; PRRT, peptide receptor radionuclide therapy; SSA, somatostatin analogues; STZ/5-FU, streptozotocin/fluorouracil; TemCap, temozolomide-capecitabine.
Current Guidelines

Management of Pancreatic NEN

- **Individualised** therapeutic plan based on evidence and patient’s characteristics (discussion in NET MDT)

**Functional activity**
- Complete resection if feasible (G1/G2)
- Non-functional (G1, low G2, low tumor burden, SD or initial diagnosis, no symptoms)
- Non-functional (G2, high tumor burden, and/or PD or symptoms)
- G3 NEN

**Advanced loco-regional disease or distant metastases**

- Diazoxide (insulinoma)
- PPI (gastrinoma)
- Octreotide or lanreotide
- IFN-alpha 2b (if SSTR negative)
- Refractory syndrome
- Consider debulking surgery of LM
- Consider locoregional/ablative therapy
- or SSA dose increase
- or add-on IFN-alpha 2b (if not already receiving)
- or everolimus (insulinoma)
- or PRRT

- Resect primary and metastases
- Everolimus or sunitinib
- or cytotoxic chemotherapy
- or locoregional therapies
- or lanreotide (octreotide if prior watch and wait)
- → PD
- → PD

- Lanreotide (octreotide) or Watch and wait
- → PD

- Cytotoxic chemotherapy
- → PD

- G3 NEC
- Cisplatin + Etoposide
- STZ/5-FU or TEM/CAP
- → PD

- G3 NEC
- FOLFOX or FOLFIRI or Clinical trial
- Everolimus or Sunitinib
- → PD

- G3 NEC
- STZ/5-FU
- PRRT or 2nd-line CTX or Clinical trial

**Advanced loco-regional disease or distant metastases**

- Cisplatin + Etoposide
- STZ/5-FU or TEM/CAP
- → PD

- FOLFOX or FOLFIRI or Clinical trial
- Everolimus or Sunitinib
- → PD

- G3 NEC
- STZ/5-FU or TEM/CAP
- → PD

- FOLFOX or FOLFIRI or Clinical trial
- Everolimus or Sunitinib
- → PD

- G3 NEC
- STZ/5-FU
- PRRT or 2nd-line CTX or Clinical trial

- *Cisplatin may be replaced by carboplatin*

CS, carcinoid syndrome; CTX, chemotherapy; FOLFIRI, folinic acid, fluorouracil and irinotecan; FOLFOX, folinic acid, fluorouracil and oxaliplatin; IFN, interferon; LM, liver metastasis; MDT, multidisciplinary team; NEC, neuroendocrine carcinoma; NEN, neuroendocrine neoplasm; NET, neuroendocrine tumour; PD, progressive disease; PPI, proton pump inhibitor; PRRT, peptide receptor radionuclide therapy; SD, stable disease; SSA, somatostatin analogues; STZ/5-FU, streptozotocin/5-Fluorouracil; TEM/CAP, temozolomide-capecitabine.

CASE 2: MR XX

- 69 years old male
- PMH: hypertension
- FMH: nil
- SH: retired, non-smoker, moderated alcohol

- Presented with abdominal pain and tiredness. Performance status 1
- January 2016: CT 7x4cm mass in the uncinate process of the pancreas; indeterminate liver lesions.
- February 2016: EUS-FNA well differentiated neuroendocrine tumour, Ki-67 = 15% (grade 2)

CT, computed tomography; EUS-FNA, endoscopic ultrasound-fine needle aspiration; FMH, family medical history; PMH, past medical history; SH, social history.
CASE 2: MR XX

- March 2016: further staging:
  - MRI liver: multiple innumerable liver metastases
  - $^{68}$ Gallium SR-PET: Receptor positive disease within bone, liver (some uptake is heterogeneous), nodal metastases, and pancreatic mass (primary). Evidence of progression compared with previous imaging

MRI, magnetic resonance imaging; SR-PET, somatostatin receptor positron emission tomography
CASE 2: MR XX

Grade 2
Metastatic Pan-NET
Widespread disease
Progressing
High tumour burden
Ga-SR PET +ve

Options:
- SSA
- Sunitinib
- Everolimus
- TemCap
- STZ/5-FU
- PRRT

Ga-SR PET, gallium somatostatin receptor positron emission tomography; Pan-NET, pancreatic neuroendocrine tumour; PRRT, peptide receptor radionuclide therapy; SSA, somatostatin analogues; STZ/5-FU, streptozotocin/fluorouracil; TemCap, temozolomide-capecitabine.
CASE 2: MR XX

Options:

- SSA
- Sunitinib
- Everolimus
- TemCap
- STZ/5-FU
- PRRT

Grade 2
Metastatic Pan-NET
Widespread disease
Progressing
High tumour burden
Ga-SR PET +ve

Ga-SR PET, gallium somatostatin receptor positron emission tomography; Pan-NET, pancreatic neuroendocrine tumour; PRRT, peptide receptor radionuclide therapy; SSA, somatostatin analogues; STZ/5-FU, streptozocin/fluorouracil; TemCap, temozolomide-capecitabine.
CASE 2: MR XX

- Zoledronic acid (widespread bone metastases)
- April-September 2016: TemCap
  - Partial response after 3 months: -32.6% RECIST 1.1
  - Maintained response after 6 months; treatment break
  - 3-monthly imaging until October 2017: stable
- December 2017: one of lesions within the liver increased in size; otherwise stable disease (1.4cm→3.2cm)
  - MDT: considered radiotherapy to liver lesion
    - Not possible due to size and further progression
    - TemCap restarted → new progression after 3 months
  - MDT: New biopsy confirmed G2 NET with areas of G3 NEC
    - Mitotic index is 22 per 10 high power fields; Ki-67 not available

MDT, multidisciplinary team; NEC, neuroendocrine carcinoma; NET, neuroendocrine tumour; RECIST, response evaluation criteria in solid tumours; TemCap, temozolomide-capecitabine.
CASE 2: MR XX

Grade 2; **areas of G3-NEC**
Metastatic Pan-NET
Widespread disease
Progressing
High tumour burden
Ga-SR PET +ve

Options:
- Everolimus
- SSA
- Sunitinib
- Platinum-Etoposide
- Other chemotherapy
- PRRT

Ga-SR PET, gallium somatostatin receptor positron emission tomography; NEC, neuroendocrine carcinoma; Pan-NET, pancreatic neuroendocrine tumour; PRRT, peptide receptor radionuclide therapy; SSA, somatostatin analogues.
CASE 2: MR XX

Options:
- Everolimus
- SSA
- Sunitinib
- **Platinum-Etoposide**
- **Other chemotherapy**
- PRRT

Grade 2; **areas of G3-NEC**
Metastatic Pan-NET
Widespread disease
Progressing
High tumour burden
Ga-SR PET +ve

Ga-SR PET, gallium somatostatin receptor positron emission tomography; NEC, neuroendocrine carcinoma; Pan-NET, pancreatic neuroendocrine tumour; PRRT, peptide receptor radionuclide therapy; SSA, somatostatin analogues.
CASE 2: MR XX

- March 2018: started Platinum-Etoposide
- New progression after 3 months
CASE 2: MR XX

Options:
- Everolimus
- Best supportive care
- PRRT
- Sunitinib
- Other

Grade 2; areas of G3-NEC
Metastatic Pan-NET
Widespread disease
Progressing
High tumour burden
Ga-SR PET +ve

Ga-SR PET, gallium somatostatin receptor positron emission tomography; NEC, neuroendocrine carcinoma; Pan-NET, pancreatic neuroendocrine tumour; PRRT, peptide receptor radionuclide therapy; SSA, somatostatin analogues.
CASE 2: MR XX

Options:

- Everolimus
- Best supportive care
- **PRRT**
- Sunitinib
- Other

Grade 2; areas of G3-NEC
Metastatic Pan-NET
Widespread disease
Progressing
High tumour burden
Ga-SR PET +ve

Ga-SR PET, gallium somatostatin receptor positron emission tomography; NEC, neuroendocrine carcinoma; Pan-NET, pancreatic neuroendocrine tumour; PRRT, peptide receptor radionuclide therapy; SSA, somatostatin analogues.
CASE 2: MR XX

- Ga-SR PET repeated: +ve disease confirmed
- PRRT:
  - #1 Sept 2018; #2 Oct 2018
  - CT scan: Stable disease → planned for #3 (cancelled)
  - Drop platelets after #2: further PRRT could not proceed
- MDT: Everolimus vs FOLFIRI
  - Feb 2019: favoured everolimus (due to myelosuppression following PRRT)
- Mar 2019: clinical deterioration
  - Best supportive care (passed away April 2019)
TAKE HOME MESSAGE

• Every patient diagnosed with Pan-NETs requires an individualised plan of treatment based on:
  – Grade
  – Disease spread / tumour burden
  – Localisation of disease
  – Symptoms
  – Performance status

• Discussion in NET MDT is warranted

MDT, multidisciplinary team; NET, neuroendocrine tumours; Pan-NETs, pancreatic neuroendocrine tumours.
SUMMARY

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## TUMOUR FEATURES IMPACT ON TREATMENT CHOICES

<table>
<thead>
<tr>
<th></th>
<th>Well differentiated</th>
<th>Poorly differentiated</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ENETS Grade</strong></td>
<td>Low (G1)</td>
<td>High (G3)</td>
</tr>
<tr>
<td><strong>Ki67 (%)</strong></td>
<td>&lt; 2%</td>
<td>&gt;20</td>
</tr>
<tr>
<td><strong>Growth (Imaging)</strong></td>
<td>No/ slowly</td>
<td>rapid</td>
</tr>
<tr>
<td><strong>Functional imaging</strong></td>
<td>SRI +ve</td>
<td>FDG PET +ve</td>
</tr>
<tr>
<td><strong>Prognosis</strong></td>
<td>Indolent</td>
<td>Poor</td>
</tr>
<tr>
<td><strong>Therapy</strong></td>
<td>Surgery</td>
<td>Chemotherapy</td>
</tr>
<tr>
<td></td>
<td>SSA</td>
<td>PRRT, Targeted drugs</td>
</tr>
<tr>
<td>Adjuvant therapy</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>
PARAMETERS WITH IMPACT ON DECISION MAKING

- Age
- ECOG PS
- Functional activity
- Elevated biomarkers
- Comorbidities

Kí67 low
Tumour burden high
Tumour burden low
Kí67 high

Slope

Nomograms for NET G1/2 and NEC

THERE IS NO SINGLE APPROACH TO TREAT PATIENTS WITH METASTATIC NEN

ALL CASES TO BE DISCUSSED IN EXPERT MDT MEETING

FDG PET, fluorodeoxyglucose-positron emission tomography; SSTR, somatostatin receptor
REACH NET CONNECT VIA TWITTER, LINKEDIN, VIMEO AND EMAIL OR VISIT THE GROUP’S WEBSITE

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