4TH ESO-ESMO-RCE
CLINICAL UPDATE ON RARE
ADULT SOLID CANCERS

29 November - 1 December 2019
Milan, Italy

Chairs:
J.Y. Blay, FR - P.G. Casali, IT - R.A. Stahel, CH

FURTHER INFORMATION AVAILABLE AT WWW.ESO.NET

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Held in collaboration with

In the framework of

COURSES AND SEMINARS
Update on neuroendocrine tumors

GASTROENTEROPANCREATIC NEUROENDOCRINE NEOPLASMS

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DISCLOSURE

◆ Personal financial interests:

◆ Institutional financial interests:
Clinical trials (P.I., Steering committee): Novartis, Ipsen, Merck Serono, MSD, Pharmacyclics, Incyte, Halozyme, Roche, Astellas, Pfizer, FivePrime, BeiGene.

◆ Non-financial interests:
ESMO: Coordinator of the Neuroendocrine, Endocrine neoplasms and CUP Faculty
ENETS: advisory board chairman
AIOM: coordinator of neuroendocrine neoplasms guidelines
ITANET: Scientific committee member
OBJECTIVES

❖ To describe terminology, epidemiology and clinical characteristics of GEP NEN

❖ To review the management of patients with advanced disease

❖ To summarize the TKIs development in GEP NETs
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❖ To describe terminology, epidemiology and clinical characteristics of GEP NEN

❖ To review the management of patients with advanced disease

❖ To summarize the TKIs development in GEP NETs
<table>
<thead>
<tr>
<th>Terminology</th>
<th>Differentiation</th>
<th>Grade</th>
<th>Mitotic rate&lt;sup&gt;a&lt;/sup&gt; (mitoses/2 mm²)</th>
<th>Ki-67 index&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>NET, G1</td>
<td>Low</td>
<td>&lt; 2</td>
<td>&lt; 3%</td>
<td></td>
</tr>
<tr>
<td>NET, G2</td>
<td>Well differentiated</td>
<td>Intermediate</td>
<td>2–20</td>
<td>3–20%</td>
</tr>
<tr>
<td>NET, G3</td>
<td>High</td>
<td>&gt; 20</td>
<td>&gt; 20%</td>
<td></td>
</tr>
<tr>
<td>NEC, small cell type (SCNEC)</td>
<td>Poorly differentiated</td>
<td>High&lt;sup&gt;b&lt;/sup&gt;</td>
<td>&gt; 20</td>
<td>&gt; 20%</td>
</tr>
<tr>
<td>NEC, large cell type (LCNEC)</td>
<td></td>
<td>High&lt;sup&gt;b&lt;/sup&gt;</td>
<td>&gt; 20</td>
<td>&gt; 20%</td>
</tr>
<tr>
<td>MiNEN</td>
<td>Well or poorly differentiated&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Variable&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Variable&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Variable&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
NETs: Incidence

Crude incidence rate in Europe
Rate x 100,000/year. Period of diagnosis 2000–2007. Error bars are 95% confidence intervals

- Rare neuroendocrine tumours
  - GEP – well differentiated not functioning endocrine carcinoma of pancreas and digestive system
  - GEP – well differentiated functioning endocrine carcinoma of pancreas and digestive system
  - GEP – poorly differentiated endocrine carcinoma of pancreas and digestive system(*)
  - GEP – mixed endocrine-exocrine carcinoma of pancreas and digestive system
- Endocrine carcinoma of thyroid gland
- Rare neuroendocrine carcinoma of skin
- Typical and atypical carcinoid of the lung
- Rare neuroendocrine carcinoma of other sites
- Rheochromocytoma malignant
- Paraganglioma

Data from www.rarecarenet.eu

Rare cancer definition < 6 new cases / 100,000 per year

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GEP NECs: epidemiology

Dasari et al., Cancer 2017
GEP NET: clinical presentation

At diagnosis mainly:

✓ **Metastatic** (mostly liver)

✓ **Non functioning** (no clinical syndrome)

✓ **Sporadic** (no genetic syndrome, like MEN-1 or VHL)

✓ **SSTR-2 positive** (at $^{68}$Ga-SSA-PET/CT)

*Cives et al., CA Cancer J Clin 2018*
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❖ To review the management of patients with advanced disease

❖ To summarize the TKIs development in GEP NETs
FDA/EMA approved therapies for patients with advanced GEP NETs

- STZ in panNET
- Octreotide IFN in carcinoid syndrome
- Lanreotide in carcinoid syndrome

Timeline:
- ‘70
- ’80
- ’90
- 2011
- 2015
- 2016
- 2017

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FDA/EMA approved therapies for patients with advanced GEP NETs

- **STZ in panNET**
- **Octreotide IFN in carcinoid syndrome**
- **Lanreotide in carcinoid syndrome**
- **Sunitinib Everolimus in panNET**
- **Octreotide in midgut**
- **Lanreotide in GEP**
- **Everolimus in non functioning Lung and GI**
- **Telotristat in refractory carcinoid syndrome diarrhea**
- **PRRT in GEP NET**

Timeline:
- 1970
- 1980
- 1990
- 2011
- 2015
- 2016
- 2017

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FDA/EMA approved therapies for patients with advanced GEP NETs

- STZ in panNET
- Octreotide IFN in carcinoid syndrome
- Lanreotide in carcinoid syndrome
- Sunitinib Everolimus in panNET
- 2011
- Octreotide in midgut
- Lanreotide in GEP
- 2015
- Everolimus in non functioning Lung and GI
- Telotristat in refractory carcinoid syndrome diarrhea
- PRRT in GEP NET
- Liver-directed treatments (surgical and not surgical)
- ‘70
- ‘80
- ‘90
- 2011
- 2015
- 2016
- 2017
- TMZ
- Oxaliplatin
Two issues

- In patients with advanced GEP NET there is no absolute evidence about a specific sequence or integration of therapies.

- No validated predictive factors for response/efficacy to some therapies are currently available in clinical practice.
SSTR-2: selection factor for PRRT
SSTR-2 grade of expression at SRS: Krenning scale

Response prediction for GEP NETs with $^{111}$In-pentetreotide uptake greater than kidney/spleen (Grade 4 of the Krenning scale) is only 60%.

Kwekkeboom et al., End Rel Cancer 2010
Bodei et al., Eur J Nucl Med Mol Imag 2018
PPQ: PRRT predictive quotient

PPQ → An algorithm that integrates blood-derived NET-specific gene transcripts (growth factor signaling and metabolic regulation) with tissue Ki67 values.

Overall the PPQ was 94% accurate for predicting responders and non-responders.

*Bodei et al., Eur J Nucl Med Mol Imag 2018*
G1-G2 GEP NETs:
Factors conditioning therapeutic decision

- Syndrome
  - Symptomatic
    - Low tumor burden
  - Asymptomatic
    - High tumor burden
- No syndrome
Factors conditioning therapeutic decision

- Body/tail
- Liver-only
- Potentially resectable

- Head
- Liver + extra-hepatic
- Never resectable
NET-dedicated multidisciplinary team (MDT)
Treatments for metastatic G1-G2 SSTR-2 + panNET: level of evidence

Phase III vs. Plb (panNET subgroup)  
Phase III vs. Plb (panNET)  
Retrospective / Phase II  
Retrospective / Phase II / Phase III vs. chemo

SSA  
Everolimus or Sunitinib  
PRRT  
Chemotherapy

Liver-directed treatments  
Primary tumor removal

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“Patients with 5–20% Ki-67 pNET can be treated with chemotherapy”

“Factors that favour chemotherapy compared with targeted therapies:

✓ Bulky disease;
✓ Symptomatic patient;
✓ Rapid tumour progression in ≤ 6–12 months;
✓ Patients with a possible chance of achieving a response to allow for surgery (neoadjuvant option)”
Progressing metastatic NF G2-G3 SSTR-2 + GEP NET

NETTER-2 trial:
PRRT
vs.
OCT LAR HD
Metastatic NF G2 SSTR-2 + panNET: 2° line therapy

?  
Chemotherapy
Sunitinib
Everolimus

COMPETE trial: Everolimus vs. PRRT
High grade GEP NENs
High grade panNENs: three categories

Overall survival of 136 patients with G3 GEP NEN according to subtype

**Type A** = well diff. + Ki-67 21-55 %

**Type B** = poorly diff. + Ki-67 21-55%

**Type C** = poorly diff. + Ki-67 > 55%

*Mos (mo)*

- Type A: 43
- Type B: 24
- Type C: 5

*Milione et al., Neuroendocrinology 2016*
Ki-67-related tumor response to platinum/etoposide in > 20% Ki-67 GEP NENs

250 pts with advanced GEP NENs

Tumor differentiation?

Sorbye H et al., Ann Oncol 2013
Nordic group retrospective series (250 pts):
tumor response to platinum/etoposide

Response rates

<table>
<thead>
<tr>
<th>Response</th>
<th>NEC High</th>
<th>NEC Low</th>
<th>NET G3</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>PR</td>
<td>26</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>SD</td>
<td>21</td>
<td>18</td>
<td>6</td>
</tr>
<tr>
<td>PD</td>
<td>33</td>
<td>11</td>
<td>4</td>
</tr>
</tbody>
</table>

Survival

- NET G3

Progression Free Survival

- NET G3
- NEC low
- NEC high

Elvebakken, ENETS 2019 Poster oral presentation
High grade GEP NENs: three categories

**NET G3**
The most common for pancreas

- **NET G3**
  - WD
  - NET > 20% Ki-67
  - As in G2 GEP NET

**NECs**
The most common for colorectal

- **NEC Low**
  - PD
  - 21-55% Ki-67
  - Alkylating-based chemotherapy

- **NEC High**
  - PD
  - > 55% Ki-67
  - Platinum/etoposide

**WD** = well differentiated; **PD** = poorly differentiated
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# Novel TKIs in GEP NETs

<table>
<thead>
<tr>
<th>Compound</th>
<th>VEGFR</th>
<th>PDGFR</th>
<th>FGFR</th>
<th>CSF1R</th>
<th>KIT</th>
<th>FLT-3</th>
<th>RET</th>
<th>MET</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>α</td>
<td>β</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sunitinib</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Pazopanib</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cabozantinib</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Lenvatinib</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Axitinib</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Surufatinib</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
</tbody>
</table>

Phase III

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Efficacy and safety analyses of the TALENT trial (GETNE 1509): A phase II study of lenvatinib in patients (pts) with advanced G1/G2 pancreatic (panNETs) and gastrointestinal (giNETs) neuroendocrine tumors

Jaume Capdevila¹, Alberto Bongiovanni², Jorge Hernando³, Francesca Spada³, Carlos Lopez⁴, Alexandre Toulé⁵, Xavier Marino⁴, Angela Lamarca⁶, Salvatore Tafutò⁷, Ana Custodie⁸, Nicola Fazio⁹, Toni Ibrahim‡

¹Vall Hebron University Hospital and Vall Hebron Institute of Oncology (VHIO), Barcelona, Español; ²Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (I.R.S.T.), Meldola; ³European Institute of Oncology, Milan; ⁴Universidade de Vigo University Hospital, Santander; ⁵Catalan Institute of Oncology (ICO), Bellvitge; ⁶The Christie NHS Foundation Trust, Manchester; ⁷Istituto Nazionale Tumori, IRCCS Fondazione G. Pascale, Naples; ⁸La Paz University Hospital, Madrid.
### PRIMARY ENDPOINT: OVERALL RESPONSE RATE (CENTRAL RADIOLOGY REVIEW)

<table>
<thead>
<tr>
<th></th>
<th>PanNETs (n=55)</th>
<th>GI-NETs (n=56)</th>
<th>Total (n=111)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with tumor assessments</td>
<td>52</td>
<td>54</td>
<td>106*</td>
</tr>
<tr>
<td>Best overall response n(%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response (CR)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>21 (40.4%)</td>
<td>10 (18.5%)</td>
<td>31 (29.2%)</td>
</tr>
<tr>
<td>Stable disease (SD)</td>
<td>29 (55.8%)</td>
<td>41 (76%)</td>
<td>70 (66%)</td>
</tr>
<tr>
<td>Progressive disease (PD)</td>
<td>2 (3.8%)</td>
<td>0</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>0</td>
<td>3** (5.5%)</td>
<td>3 (2.8%)</td>
</tr>
</tbody>
</table>

*Five patients withdrew the informed Consent before the first post-basal tumor assessment.

**Central radiologist confirms that 3 patients did not have evaluable target lesions. They have been considered as not evaluable.
PROGRESSION-FREE SURVIVAL

PFS (gastrointestinal tumors)

Median = 15.4 months

PFS (pancreatic tumors)

Median = 15.6 months
#4979 Efficacy and Safety of Surufatinib in Patients with Well-Differentiated Advanced Extrapancreatic Neuroendocrine Tumors (NETS)

Results from the randomized phase III study (SANET-ep) (NCT02588170)
SANET-ep: PHASE III STUDY DESIGN

Study population
Progressive, advanced extrapancreatic NET

Randomization: 2:1
Stratification factors
- Treated or naive
- Pathological grade 1 or 2
- Tumor origins A, B or C

Surufatinib 300mg QD
Survival follow up

Placebo
Open-label surufatinib

Primary Endpoint:
- Investigator-assessed PFS

Secondary Endpoints:
- ORR, DCR, DoR, TTR, OS
- Safety and tolerability
INVESTIGATOR-ASSESSED PFS (PRIMARY)

SANET-ep clearly succeeded in meeting the superiority criteria of PFS.

**Median PFS**
- **Surufatinib**: 9.2 months (95% CI 7.4, 11.1)
- **Placebo**: 3.8 months (95% CI 3.7, 5.7)
- **Stratified HR**: 0.334 (95% CI 0.223, 0.499)
  \[ p < 0.0001 \]

Statistical assumption: 273 patients planned based on the assumption of the median PFS of 8 months in placebo arm, HR of surufatinib treatment is 0.6 with a two sided alpha 0.05.
### Most Common TEAEs with Frequency ≥ 20% (Safety Analysis Set)

<table>
<thead>
<tr>
<th>TEAEs</th>
<th>Surufatinib (N=129)</th>
<th>Placebo (N=68)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any grade</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>91 (70.5)</td>
<td>25 (19.4)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>83 (64.3)</td>
<td>47 (36.4)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>60 (46.5)</td>
<td>2 (1.6)</td>
</tr>
<tr>
<td>Blood thyroid stimulating hormone increased</td>
<td>51 (39.5)</td>
<td>0</td>
</tr>
<tr>
<td>Blood bilirubin increased</td>
<td>50 (38.8)</td>
<td>3 (2.3)</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>47 (36.4)</td>
<td>5 (3.9)</td>
</tr>
<tr>
<td>Fecal occult blood positive</td>
<td>46 (35.7)</td>
<td>0</td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>41 (31.8)</td>
<td>3 (2.3)</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>37 (28.7)</td>
<td>0</td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>32 (24.8)</td>
<td>4 (3.1)</td>
</tr>
<tr>
<td>Abdominal pain upper</td>
<td>29 (22.5)</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Anemia</td>
<td>27 (20.9)</td>
<td>9 (7.0)</td>
</tr>
</tbody>
</table>
CLOSING REMARKS

✓ Although many different treatments are available no therapeutic sequence or integration has been validated so far for tumor growth control

✓ Therefore GEP NET patients should be preferably managed involving a NEN referral Centers with a NEN-dedicated MDT

✓ Predictive factors of response/efficacy are an urgent unmet need
European Institute of Oncology, ENETS CoE

IEO NEN MDT

Thanks!