ESMO PRECEPTORSHIP PROGRAMME
NEUROENDOCRINE NEOPLASMS

Multidisciplinary management, standards of care and future perspectives

Lugano, Switzerland
13-14 April 2018

CHAIR: Nicola Fazio, Italy
George Pentheroudakis, Greece

SPEAKERS: Pier Luigi Filosso, Italy
Andrea Frilling, United Kingdom
Rocio Garcia-Carbonero, Spain
Massimo Milione, Italy
Marianne Pavel, Germany
Aviral Singh, Germany
Anders Sundin, Sweden
Christos Toumpanakis, United Kingdom

Ongoing and future clinical investigation in GEP NENs

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Disclosure

Novartis, Ipsen, Pfizer, AAA, Merck Serono: consulting and advisory services

Novartis, Merck Serono: Research funds (to the institution)
Investigation lines in GEP NENs

- SSA
- Sequence
- PRRT
- High grade
- New drugs
- Immunotherapy
Investigation lines in GEP NENs

- SSA
  - Sequence
  - PRRT
  - High grade
  - New drugs
  - Immunotherapy
Efficacy and Safety of Lanreotide Autogel® 120 mg Administered Every 14 Days in WellDifferentiated, Metastatic or LocallyAdvanced, Unresectable Pancreatic or Midgut NeuroendocrineTumours Having Progressed Radiologically While PreviouslyTreated With Lanreotide Autogel® 120 mg Administered Every 28Days

CLARINET FORTE

Histopathologically confirmed, grade 1 or 2, metastatic or locally advanced,unresectable pNET (pNET cohort) or midgut NET (midgut cohort) with or withouthormone related syndromes,with a proliferation index (Ki67) ≤20%.

Positive somatostatin receptors type 2

100 patients
European, prospective, multicentre, double-blind randomised study evaluating lanreotide **Lanreotide as Maintenance Therapy** in Patients With Non-Resectable Duodeno-Pancreatic Neuroendocrine Tumors 

(REMINET)

**Inclusion criteria:**
Documented stable disease or objective response after first-line treatment (chemotherapy or biotherapy for 6 months), within 4 weeks (28 days) prior to randomisation

**Treatment:**
Lanreotide 120 mg every 28 days until disease progression versus placebo
Investigation lines in GEP NENs

- SSA
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- Immunotherapy
GETNE 1206 (SEQUTOR) phase III trial in patients with advanced panNETs enrolling

**Primary end point:** rate of second PFS at 84 weeks of treatment
Investigation lines in GEP NENs

- SSA
- Sequence
- **PRRT**
- High grade
- New drugs
- Immunotherapy
A prospective, randomised, **Controlled, Open-label, Multicentre phase III** study to evaluate efficacy and safety of Peptide Receptor Radionuclide Therapy (PRRT) with $^{177}$Lu-Edotreotide compared to targeted molecular therapy with **Everolimus** in patients with inoperable, progressive, somatostatin receptor-positive (SSTR+), neuroendocrine tumours of gastroenteric or pancreatic origin (GEP- NET).

**COMPETE trial**

G1-G2 advanced progressive GEP NET

**Rand. Phase III**

$^{177}$Lu-edotreotide

Everolimus
Initiated & Sites Ready for Initiation
- Australia, Austria, France, Germany, Netherlands, South Africa, Switzerland, UK

Review in progress
- Italy, Poland

EC / CA submissions to be done
- US
Investigation lines in GEP NENs

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- High grade
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- Immunotherapy
Phase II trial
Everolimus and Temozolomide
in Advanced GEP NECs (G3)

Histologically proven neuroendocrine carcinoma with a Ki67 of 20-55%.
Primary GEP NET or unknown primary where metastases are mainly abdominal
Randomized phase II study of cisplatin and etoposide versus temozolomide and capecitabine in patients (pts) with advanced G3 non-small cell gastroenteropancreatic neuroendocrine carcinomas (GEPNEC): A trial of the ECOG-ACRIN Cancer Research Group (EA2142).

G3 (only large cell) GEP NEC
Ki-67 21-100%
First-line

Rand. Phase II
126 pts
Prospective International Phase II Multi-centre Trial

\(^{177}\text{Lu-DOTA-octreotate (LuTate) PRRT Vs Capecitabine Temozolomide chemotherapy for Grade 3 GEP NEN (Ki67 20-55\%) – LUCAT Trial}

PI: Grace Kong, Michael Michael, Rod Hicks
Peter MacCallum Cancer Center, Melbourne, Australia

- **Primary objective** – PFS.
- **56 patients**

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**LuCAT Trial**
- Patients with G3 NEN with Ki67 of 20-55%
- SSTR positive on GaTate PET/CT
- No Spatially discordant FDG-avid disease

**LuTate PRRT**
- PRRT up to 4 cycles, 8 weekly
- Restage with GaTate, FDG, CT 8 weeks after last cycle (32 wks)

**CAPTEM chemotherapy**
- Capecitabine Day 1-14, Temozolomide Day 10-14 Up to 6 cycles, 4 weekly
- Restage with CT 6 weeks after last cycle;
- GaTate, FDG, CT 12 weeks after last cycle (32 weeks)
Investigation lines in GEP NENs

- SSA
- Sequence
- PRRT
- High grade
- New drugs
- Immunotherapy
# 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>
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<tbody>
<tr>
<td></td>
<td>1 2 3</td>
<td>α β</td>
<td></td>
<td></td>
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<tr>
<td><strong>Sunitinib</strong></td>
<td>✔ ✔ ✔ ✔</td>
<td></td>
<td></td>
<td>✔</td>
<td></td>
<td>✔ ✔ ✔</td>
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<tr>
<td><strong>Pazopanib</strong></td>
<td>✔ ✔ ✔ ✔</td>
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<td></td>
<td></td>
<td>✔</td>
<td></td>
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<tr>
<td><strong>Cabozantinib</strong></td>
<td>✔ ✔ ✔ ✔</td>
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<td></td>
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<td></td>
<td>✔ ✔ ✔</td>
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<tr>
<td><strong>Lenvatinib</strong></td>
<td>✔ ✔ ✔ ✔</td>
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<td>✔</td>
<td></td>
<td>✔ ✔ ✔</td>
<td></td>
<td>✔</td>
</tr>
<tr>
<td><strong>Sulfatinib</strong></td>
<td>✔ ✔ ✔ ✔</td>
<td></td>
<td>✔ ✔ ✔</td>
<td></td>
<td></td>
<td>✔</td>
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</tbody>
</table>
Sulfatinib in GEP NET

81 NET pts (41 pNET)
Sulfatinib in GEP NET

Progression free survival in ITT patients as of 20 Jan 2017

- All patients: 16.6 m (95% CI 13.4, 19.4)
- PNET group: 19.4 m (95% CI 13.8, 22.1)
- EP-NET group: 13.4 m (95% CI 7.6, 16.7)

Among 41 PNET patients: 18 (43.9%) still on treatment; 7 (17.1%) discontinued due to AE or withdrawal; 16 (39.0%) experienced PD/death.

<table>
<thead>
<tr>
<th>Event</th>
<th>N=81 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>81 (100)</td>
</tr>
<tr>
<td>Grade ≥3 AE</td>
<td>63 (77.8)</td>
</tr>
<tr>
<td>Any SAE</td>
<td>21 (25.9)</td>
</tr>
<tr>
<td>Any drug-related AE</td>
<td>81 (100)</td>
</tr>
<tr>
<td>Any drug-related grade ≥3 AE</td>
<td>58 (71.6)</td>
</tr>
<tr>
<td>Any drug related SAE</td>
<td>10 (12.3)</td>
</tr>
<tr>
<td>Drug related AE leading to:</td>
<td></td>
</tr>
<tr>
<td>- dose interruption</td>
<td>40 (49.4)</td>
</tr>
<tr>
<td>- dose reduction</td>
<td>20 (24.7)</td>
</tr>
<tr>
<td>- drug withdrawal</td>
<td>7 (8.6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Event</th>
<th>Grade ≥3 (≥4pts) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>25 (30.9)</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>11 (13.6)</td>
</tr>
</tbody>
</table>

Jia, ENETS 2017, Oral presentation
Cabozantinib in GEP NET

Phase II trial

41 carcinoids
- PR: 15%
- SD: 63%
- mPFS: 31 mo

20 pNETs
- PR: 15%
- SD: 75%
- mPFS: 22 mo

Chan et al., ASCO GI 2017, Poster
TALENT trial
Phase II with LENVATINIB in GEP NETs

Lenvatinib binds to
RET, VEGFR and FGFR

- Pancreatic G1/G2 cohort (n=55)
- Gastrointestinal G1/G2 cohort (n=55)

Accrual completed

Recruitment Graph
Table 1. Inhibitory concentrations (IC50 in nmol) for targets with multtargeted TKIs.

<table>
<thead>
<tr>
<th>Drug</th>
<th>VEGFR1</th>
<th>VEGFR2</th>
<th>VEGFR3</th>
<th>PDGFRα</th>
<th>PDGFRβ</th>
<th>c-Kit</th>
<th>RET</th>
<th>RAF</th>
<th>FLT3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axitinib⁹</td>
<td>0.1</td>
<td>0.2</td>
<td>0.1–0.3</td>
<td>5</td>
<td>1.6</td>
<td>1.7</td>
<td>&gt;1000</td>
<td>NA</td>
<td>&gt;1000</td>
</tr>
<tr>
<td>Pazopanib²⁴</td>
<td>10</td>
<td>30</td>
<td>47</td>
<td>71</td>
<td>84</td>
<td>74</td>
<td>&gt;1000</td>
<td>NA</td>
<td>&gt;1000</td>
</tr>
<tr>
<td>Sunitinib²⁵</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>5–10</td>
<td>10</td>
<td>13</td>
<td>100–200</td>
<td>NA</td>
<td>1–10</td>
</tr>
<tr>
<td>Sorafenib²⁶</td>
<td>NA</td>
<td>90</td>
<td>20</td>
<td>50–60</td>
<td>50–60</td>
<td>68</td>
<td>100–150</td>
<td>5–10</td>
<td>46</td>
</tr>
</tbody>
</table>

Axitinib is highly bound (99%) to human 1-acid glycoprotein. As a measure of precaution, antacids or proton pump inhibitors should be administered at times other than 2 h before and 2 h after drug dosing. The oral bioavailability of axitinib is 58%. Although a low pH results in the highest solubility of axitinib, studies have demonstrated that the effect of pH on absorption of axitinib was not clinically justifying the need for dose reduction in patients with decreased gastric pH (versus 6–880 nmol/L (versus 6–880 nmol/L (versus 6–880 nmol/L (versus 6–880 nmol/L)).

**VEGF-B**

**VEGF-C**

**VEGF-D**

**VEGF-E**

**VEGF-A**

**VEGF-F**

**VEGF-G**

**VEGF-H**

**VEGF-I**

**VEGF-J**

**VEGF-K**

**VEGF-L**

**VEGF-M**

**VEGF-N**

**VEGF-O**

**VEGF-P**

**VEGF-Q**

**VEGF-R**

**VEGF-S**

**VEGF-T**

**VEGF-U**

**VEGF-V**

**VEGF-W**

**VEGF-X**

**VEGF-Y**

**VEGF-Z**

**AXITINIB**
A PHASE II/III RANDOMIZED DOUBLE-BLIND STUDY OF SANDOSTATIN LAR IN COMBINATION WITH AXITINIB VERSUS SANDOSTATIN LAR WITH PLACEBO IN PATIENTS WITH ADVANCED G1-G2 NEUROENDOCRINE TUMOURS (WHO 2010) OF NON-PANCREATIC ORIGIN

N = 253

Nonpancreatic G1-G2 NETs with progression of disease in the previous 12 mo

- ECOG PS 0-2
- Age ≥ 18 years
- With or without previous chemotherapy
- Ki67 < 20%

* RANDOMIZATION

Arm A: Axitinib + Sandostatin LAR

Arm B: Placebo + Sandostatin LAR
CDK 4/6 inhibitors in NETs
**CDK 4/6 inhibition in NET:**
*preclinical studies with ribociclib and pabociclib*

**CDK4/6 controls cell cycle progression from G1 to S phase by regulating the activity of Rb**

Tang L. et al., *Clin Cancer Res* 2012
Ribociclib in NET: preclinical study

Ribociclib sensitivity was associated with high expression of cyclin-1 and Rb

Ribociclib/Everolimus or 5-FU combinations were superior to the single-agent therapies, by downregulating mTOR and MEK pathways

Prada et al, Neuroendocrinology 2016
A phase II trial of palbociclib in metastatic grade 1/2 pancreatic neuroendocrine tumors: the PALBONET study on behalf of the Spanish Taskforce Group of Neuroendocrine Tumors (GETNE)

Enrique Grande1, Alexandre Teulé2, Teresa Alonso-Gordoa1, Paula Jiménez-Fonseca3, Marta Benavent4, Jaume Capdevila5, Ana Custodio6, Ruth Vera7, Javier Munárriz8, Adelaida La Casta-Muñoa9, Rocío García-Carbonero10

<table>
<thead>
<tr>
<th>Patients treated</th>
<th>21</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>0</td>
</tr>
<tr>
<td>Stable disease (SD)</td>
<td>11</td>
</tr>
<tr>
<td>Progression disease (PD)</td>
<td>9</td>
</tr>
</tbody>
</table>

mPFS: 2.6 months (95% CI 0–14.4)
A Phase II Study of LEE011 (Ribociclib) in Patients with Advanced Neuroendocrine Tumors of Foregut Origin (CLEE011 XUS02T)

US only
Research lines in GEP NENs

- SSA
- PRRT
- High grade
- New drugs
- Immunotherapy
Molecular biology of NETs
NETs have low mutational burden
PDR001 in GEP and Lung NET/NEC

*Phase II multi-cohort international study*

PDR001 binds to PD-1 so blocking both PD-L1 and PD-L2

- Well differentiated:
  - GI cohort (n=20)
  - Pancreatic cohort (n=20)
- Poorly differentiated:
  - GEP cohort (n=20)

Accrual completed
A multicohort phase II study of **durvalumab plus tremelimumab** for the treatment of patients (PTS) with advanced neuroendocrine neoplasms (NENs) of gastroenteropancreatic (GEP) or lung origin (the DUNE trial-GETNE1601-).

**Single-arm Phase II**

126 pts

- Well differentiated:
  - GI cohort (n=30)
  - Pancreatic cohort (n=30)
  - Thoracic cohort (n=30)

- Poorly differentiated:
  - GEP cohort (n=20)
European Institute of Oncology, IEO, Milan, Italy
ENETS Center of Excellence for GEP NETs
IEO NET MDT

Thanks!