Clinical management of intermediate grade GEP NENs

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**DISCLOSURES**

- **Personal financial interests:** Novartis, Ipsen, Pfizer, Merck Serono, Advanced Accelerator Applications, MSD (Advisory board, public speaking)

- **Institutional financial interests:** Novartis, Ipsen, Merck Serono, MSD, Pharmacyclics, Incyte, Halozyrne, Roche, Astellas, Pfizer (Clinical trials or research projects: principal investigator, steering committee member)

- **Non-financial interests:**
  - ESMO: Coordinator of the Neuroendocrine, Endocrine neoplasms and CUP Faculty
  - ENETS: advisory board chairman
  - AIOM: coordinator for ITALIAN NEN guidelines
  - ITANET: Scientific committee member
Neuroendocrine neoplasms (NENs)
Terminology

Low grade
(well differentiated, Ki-67 <3%)

Intermediate grade
(well or moderately differentiated, Ki-67 3-20%)

High grade
(Moderately diff. or poorly diff., Ki-67 > 20%)

Tumours (NETs)

Carcinomas (NECs)
WHO 2010 **GI** NEN classification

| NET (Tumours) | G1  
(Ki-67 ≤ 2% and/or MI < 2) |
|---------------|---------------------------|
| NEC (Carcinomas) | G2  
(Ki-67 3-20% and/or MI 2-20) |
|               | G3  
(Ki-67 > 20% and/or MI > 20) |
**WHO 2017 Pancreatic NEN classification**

<table>
<thead>
<tr>
<th>NET (Tumours)</th>
<th>G1 ((\text{Ki-67} \leq 2% \text{ and/or MI} &lt; 2))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>G2 ((\text{Ki-67 3-20}% \text{ and/or MI 2-20}))</td>
</tr>
<tr>
<td></td>
<td>G3 ((\text{Ki-67} &gt; 20% \text{ and/or MI} &gt; 20))</td>
</tr>
<tr>
<td>NEC (Carcinomas)</td>
<td>G3 ((\text{Ki-67} &gt; 20% \text{ and/or MI} &gt; 20))</td>
</tr>
</tbody>
</table>
Dasari et al., JAMA Oncol 2017
PanNET: G1 or G2?

**US-guided liver biopsy:**
“well-diff. NET”
Ki-67 = 10%

**Abdominal CT-scan**

**EUS-FNA:**
NET, Ki-67 2%
Ileal NET: G1 or G2?

Abdominal US: several liver focal lesions
Chest-Abdomen CT: confirmed liver lesions + mesenteric mass

Well diff. NET, 15% Ki-67
Well diff. NET, 2% Ki-67
Metastatic ileal NET

Liver mets from ileal NET

Ki-67 1%

Ki-67 10%

Ki-67 20%

SSA ?

PRRT ?

EVE ?
Metastatic NF G2 SSTR-2 + small bowel NET

Clinical trials

Primary tumor removal

Liver-directed treatments

Everolimus

PRRT

SSA

1 2 3 4 5
Midgut well differentiated NET: SSA as first-line therapy

SSA
- Octreotide LAR 30 mg/4w
- Lanreotide autogel 120 mg/4w

PROMID trial
- SSTR +++
- Ki-67 < 3%

CLARINET trial
- Ki-67 < 11%
- SSTR +++
RADIANT-4 trial: Grade 1 vs Grade 2 NETs

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Everolimus N = 205</th>
<th>Placebo N = 97</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1 / grade 2</td>
<td>63% / 37%</td>
<td>67% / 33%</td>
</tr>
<tr>
<td>Metastatic extent of disease¹</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>80%</td>
<td>78%</td>
</tr>
<tr>
<td>Lymph node or lymphatic system</td>
<td>42%</td>
<td>46%</td>
</tr>
<tr>
<td>Lung</td>
<td>22%</td>
<td>21%</td>
</tr>
<tr>
<td>Bone</td>
<td>21%</td>
<td>16%</td>
</tr>
<tr>
<td>Median time from initial diagnosis to randomization, months (range)</td>
<td>29.9 (0.7-258.4)</td>
<td>28.9 (1.1-303.3)</td>
</tr>
<tr>
<td>Median time from most recent progression until enrolment, months (range)²</td>
<td>1.68 (0.0-7.8)</td>
<td>1.45 (0.2-11.8)</td>
</tr>
<tr>
<td>Prior treatments</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somatostatin analogues</td>
<td>53%</td>
<td>56%</td>
</tr>
<tr>
<td>Surgery</td>
<td>59%</td>
<td>72%</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>26%</td>
<td>24%</td>
</tr>
<tr>
<td>Radiotherapy including PRRT</td>
<td>22%</td>
<td>20%</td>
</tr>
<tr>
<td>Locoregional and ablative therapies</td>
<td>11%</td>
<td>10%</td>
</tr>
</tbody>
</table>

¹Organs as per target and non-target lesion locations observed at baseline by central radiology review.
²Patients were expected to have disease progression in ≤ 6 months prior to enrolment as per inclusion criteria. Protocol deviation was reported in 7 patients.

Yao J et al. Lancet, 2018
stratum A [better prognosis]:
appendix, caecum, jejunum, ileum, duodenum, or
neuroendocrine tumour of unknown primary origin

vs

stratum B [worse prognosis]:
lung, stomach, colon [other than caecum], or rectum

Yao J et al. Lancet, 2018
RADIANT-4:
results in GI subgroup (midgut + non-midgut)

Kaplan-Meier medians
Everolimus: 13.14 months (95% CI, 9.23-17.28)
Placebo: 5.36 months (95% CI, 3.58-9.30)
HR (95% CI): 0.56 (0.37; 0.84)

PFS = 13 vs. 5 mo

Singh s. et al. Neuroendocrinology, May 2017
RADIANT-4: less benefit in the ileum subgroup

In MIDGUT 6.4-month prolongation in PFS in favor of EVE = 29% of reduction of risk of progression or death.

In NON-MIDGUT 6.2-month increase in the median PFS over placebo = 73% reduction in the risk of progression or death.

Singh s. et al. Neuroendocrinology, May 2017
**Midgut NETS - ENETS 2016 guidelines**

Pavel et al, Neuroendocrinology 2016
mPFS in the control arm (OCT LAR 60 mg/4w) of the NETTER-1 trial

**Bad or good option for this patient?**

**Tumor characteristics**
- Small bowel NET
- Well differentiated
- Ki-67 5%
- SRS or Ga-PET ++

**Patient characteristics**
- P.S. = 0 (ECOG)
- Asymptomatic
- No comorbidity

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**24 months**

**CT-scan**

| SSA |

**PD RECIST**
NETTER-1 trial (229 patients)

Strosberg et al., NEJM 2017
PRRT: favourable points compared with chemotherapy and molecular targeted agents

- Very good subjective tolerability
- Selected population
- SSTR-2 expression as a potential predictive factor
PanNET: G1 vs. G2 related to the same liver tumor load

- Ki-67 1%
- Ki-67 10%
- Ki-67 20%

Options:
- SSA ?
- EVE/SUN/PR RT ?
- Chemo ?
Non functioning advanced panNET: first-line therapy

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Type of study</th>
<th>Patients with panNET</th>
<th>1° line</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLARINET</td>
<td>LANREOTIDE</td>
<td>Phase III</td>
<td>91/229</td>
<td>Caplin NEJM 2014</td>
</tr>
<tr>
<td>NCT01525550</td>
<td>SUNITINIB</td>
<td>Phase IV</td>
<td>106/106</td>
<td>Raymond Neuroend 2018</td>
</tr>
</tbody>
</table>

Nicola Fazio, M.D., Ph.D.  
IEO, European Institute of Oncology, IRCCS, Milan
# Non functioning advanced panNET: different tumor populations

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Type of study</th>
<th>PFS placebo arm</th>
<th>PFS Sunitinib arm</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLARINET</td>
<td>LANREOTIDE</td>
<td>Phase III</td>
<td>18 mo</td>
<td>Caplin NEJM 2014</td>
</tr>
<tr>
<td>NCT01525550</td>
<td>SUNITINIB</td>
<td>Phase IV</td>
<td></td>
<td>Raymond Neuroend 2018</td>
</tr>
</tbody>
</table>

*CLARINET* - Phase III, 18 mo
*NCT01525550* - Phase IV, 12 mo

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*Nicola Fazio, M.D., Ph.D.*  
*IEO, European Institute of Oncology, IRCCS, Milan*
### Supplementary Table S1. Patient demographics and baseline characteristics (full analysis set)

<table>
<thead>
<tr>
<th></th>
<th>Treatment-naive cohort</th>
<th>Previously treated cohort</th>
<th>Total population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ki-67 index</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>5.0 (0.0–20.0)</td>
<td>5.0 (0.5–30.0)</td>
<td>5.0 (0.5–30.0)</td>
</tr>
<tr>
<td>&lt;3%, n (%)</td>
<td>12 (19.7)</td>
<td>12 (26.7)</td>
<td>24 (22.6)</td>
</tr>
<tr>
<td>3%–20%, n (%)</td>
<td>49 (80.3)</td>
<td>30 (66.7)</td>
<td>79 (74.5)</td>
</tr>
<tr>
<td>&gt;20%, n (%)</td>
<td>0</td>
<td>3 (6.7)</td>
<td>3 (2.8)</td>
</tr>
</tbody>
</table>
Clarinet trial: panNET subgroup

<table>
<thead>
<tr>
<th></th>
<th>Lanreotide depot (n=42)</th>
<th>Placebo (n=49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD) in years</td>
<td>63.8 (9.1)</td>
<td>63.7 (9.2)</td>
</tr>
<tr>
<td>Male</td>
<td>26 (62)</td>
<td>29 (59)</td>
</tr>
<tr>
<td>Time since diagnosis, mean (SD) in months</td>
<td>30.4 (36.7)</td>
<td>42.1 (50.1)</td>
</tr>
<tr>
<td>Previous therapy</td>
<td>9 (21)</td>
<td>12 (24)</td>
</tr>
<tr>
<td>Previous chemotherapy</td>
<td>8 (19)</td>
<td>11 (22)</td>
</tr>
<tr>
<td>Previous surgery</td>
<td>18 (43)</td>
<td>17 (35)</td>
</tr>
<tr>
<td>Tumor progression</td>
<td>3 (7)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Tumor grade:* G1/G2</td>
<td>25 (60)/17 (40)</td>
<td>32 (65)/16 (33)</td>
</tr>
<tr>
<td>HTL: &gt;25%</td>
<td>19 (45)</td>
<td>15 (31)</td>
</tr>
</tbody>
</table>

*Ki-67 thresholds stated as per World Health Organization 2010 classification, with patients with Ki-67 values >2% and ≤10% in the present study assigned to grade 2. HTL, hepatic tumor load.

Phan et al., ASCO GI 2017
TEM alone or CAP-TEM in PanNET?

**Progression Free Survival**

<table>
<thead>
<tr>
<th></th>
<th>Median (mo)</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: Temo</td>
<td>14.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B: Temo+ Cape</td>
<td>22.7</td>
<td>0.58 (0.36, 0.93)</td>
<td>0.023</td>
</tr>
</tbody>
</table>

**Response Rates**

<table>
<thead>
<tr>
<th></th>
<th>Temo (N=72)</th>
<th>Temo + Cape (N=72)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>2.8%</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Partial response</td>
<td>25.0%</td>
<td>33.3%</td>
<td></td>
</tr>
<tr>
<td>Stable disease</td>
<td>40.3%</td>
<td>40.6%</td>
<td></td>
</tr>
<tr>
<td>Progressive disease</td>
<td>19.4%</td>
<td>13.9%</td>
<td></td>
</tr>
<tr>
<td>Unrevaluable</td>
<td>12.5%</td>
<td>4.2%</td>
<td></td>
</tr>
<tr>
<td>Objective Response Rate (CR+PR)</td>
<td>27.8%</td>
<td>33.3%</td>
<td>0.47</td>
</tr>
<tr>
<td>Disease Control Rate (CR+PR+SD)</td>
<td>68.1%</td>
<td>81.9%</td>
<td></td>
</tr>
<tr>
<td>Response Duration (median)</td>
<td>9.7 mo</td>
<td>12.1 mo</td>
<td></td>
</tr>
</tbody>
</table>

**Baseline characteristics (2)**

<table>
<thead>
<tr>
<th>Time from Diagnosis (months)</th>
<th>Temo (N=72)</th>
<th>Temo + Cape (N=72)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO Grade</td>
<td>24.4 mo</td>
<td>34.0 mo</td>
</tr>
<tr>
<td>Low (Grade 1)</td>
<td>45.1%</td>
<td>68.1%</td>
</tr>
<tr>
<td>Intermediate (Grade 2)</td>
<td>54.9%</td>
<td>31.9%</td>
</tr>
<tr>
<td>Sites of Metastasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>93.1%</td>
<td>93.1%</td>
</tr>
<tr>
<td>Bone</td>
<td>12.5%</td>
<td>11.1%</td>
</tr>
<tr>
<td>Lung</td>
<td>6.9%</td>
<td>13.9%</td>
</tr>
<tr>
<td>Peritoneum</td>
<td>5.6%</td>
<td>9.7%</td>
</tr>
<tr>
<td><strong>Prior Treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Everolimus</td>
<td>34.7%</td>
<td>36.1%</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>12.5%</td>
<td>11.1%</td>
</tr>
<tr>
<td><strong>Concurrent SSA</strong></td>
<td>54.2%</td>
<td>52.8%</td>
</tr>
</tbody>
</table>

* Imbalance (p<0.013); **Stratification factor.

Kunz, ASCO 2018 oral presentation
ENETS 2016 guidelines in distant metastases of panNET

- Non-functional (G1, low G2<sup>6</sup>, low tumor burden, SD or initial diagnosis, no symptoms)
  - Lanreotide (Octreotide) or Watch & Wait
  - Everolimus or Sunitinib or Cytotoxic chemotherapy or loco-regional therapies
  - Lanreotide (Octreotide) (if prior Watch & Wait)

- Non-functional (G2, high tumor burden, and/or PD or symptoms)
  - Cytotoxic chemotherapy
  - Everolimus or Sunitinib

- PD

- PRRT** or 2nd line CTX or Clinical trial
Pan NET: G1 vs. G2 related to two different liver tumor load

Ki-67 18%
SSTR +/-

Chemo?

Ki-67 1%
SSTR +++

SSA + PRRT?
Liver-metastatic pancreatic G2 NET: Inhomogeneous functional imaging can affect therapeutic strategy
Advanced GEP NETs: goals of treatment

- Syndrome
- Cytoreduction
- Tumour growth control (long-term stabilization)
Minimal consensus statement:

Everolimus or sunitinib are generally recommended after failure of SSA or chemotherapy in pancreatic NET.

Everolimus and sunitinib can be considered a first line therapy, especially if SSA is not an option, and if systemic chemotherapy is not clinically required, not feasible or not tolerated.

Pavel et al., Neuroendocrinology Jan 2016
Everolimus
Sunitinib
PRRT
Chemotherapy

Liver-directed treatments
Primary tumor removal

Clinical trials

Metastatic NF G2 SSTR-2 + panNET
Predictive Markers of Response to Everolimus and Sunitinib in Neuroendocrine Tumors

Diana Martins¹ & Francesca Spada¹ & Ioana Lambescu¹ & Manila Rubino¹ & Chiara Cella¹ & Bianca Gibelli² & Chiara Grana³ & Dario Ribeiro⁴ & Emilio Bertani⁴ & Davide Ravizza⁵ & Guido Bonomo⁶ & Luigi Funicelli⁷ & Eleonora Pisa⁸ & Dario Zerini⁹ & Nicola Fazio¹ & IEO ENETS Center of Excellence for GEP NETs

No validate predictive biomarker for sunitinib and everolimus so far

Martins et al., Targeted Oncol 2017
In Eastern mythology, the swan, or *hamsa*, is perceived to have a legendary power of separating milk from water when mixed together, which makes it worthy of being accompanied by the Hindu goddess of knowledge and wisdom, named *Saraswati*. The mythical power of the swan is perhaps a subtle allegory for one of the essential traits every human being must strive to possess, that is, discrimination between the real and the unreal.
This is even more important in the 21st century as we are witnessing an information overload in several scientific disciplines, including biomedicine, which is further amplified by the ease of disseminating information. A 2010 article in *PLoS Medicine* had highlighted the fact that each day, 75 clinical trials and 11 systematic reviews were being added to the medical literature at that time, with no signs of a plateau in the publication rate. A quick review of MEDLINE indexing statistics reveal that more than 5,000 journals were indexed in the year 2017, with more than 24 million citations. Even in subspecialties like medical oncology and

Finally, there is no substitute for an experienced and astute clinical mentor who can guide us in the art of critically appraising data from a trial or an observational study in the context of a patient and the clinical scenario. No textbooks or journal articles can accomplish that. We all should actively seek such mentors in the clinic.