MEETING SUMMARY
UPDATE FROM ENETS 2019
Barcelona, Spain

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CLINICAL IMPACT OF THE WHO CLASSIFICATION 2017
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NEW WHO CLASSIFICATION
PERREN, A. ORAL PRESENTATION, ENETS 2019

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CONSEQUENCES FOR TREATMENT
SORBYE, H. ORAL PRESENTATION, ENETS 2019

Lloyd, RV et al. WHO Classification of Tumours of Endocrine Organs, IARC Press, Lyon, 2017
BACKGROUND

• GEP NEN are classified into three groups based on mitotic activity and Ki-67 index in the WHO 2010 classification.\(^1\) It included three distinct groups:
  – well-differentiated NET (G1 or G2)
  – poorly-differentiated NEC G3
  – mixed adenoneuroendocrine carcinomas (MANEC)

• New observations and publications provided new understanding into PanNEN, which prompted the new WHO update in 2017\(^2\)
  – key changes and clinical implications are presented
  – publication of the fifth edition of the WHO Classification of Tumours of the Digestive System is expected in April 2019

GEP, gastroenteropancreatic; NEC, neuroendocrine carcinomas; NEN, neuroendocrine neoplasm; NET, neuroendocrine tumours; PanNEN, pancreatic neuroendocrine neoplasm; WHO, world health organisation.

### COMPARISON OF RECENT WHO CLASSIFICATIONS

#### For pancreatic NENs

<table>
<thead>
<tr>
<th></th>
<th>Ki-67 index</th>
<th>Mitotic index</th>
<th>Ki-67 index</th>
<th>Mitotic index</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Well differentiated NETs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NET G1</td>
<td>≤2%</td>
<td>&lt; 2/10 HPF</td>
<td>NET G1</td>
<td>&lt;3%</td>
</tr>
<tr>
<td>NET G2</td>
<td>3%-20%</td>
<td>2-20/10 HPF</td>
<td>NET G2</td>
<td>3%-20%</td>
</tr>
<tr>
<td>NET G3</td>
<td>&gt;20%</td>
<td>&gt;20/10 HPF</td>
<td>NET G3</td>
<td>&gt;20%</td>
</tr>
</tbody>
</table>

| **Poorly differentiated NECs** |             |               |             |               |
| NEC G3                 | >20%        | >20/10 HPF    | NEC G3      | >20%          |

| **Mixed adenoneuroendocrine carcinoma (MANEC)** |             |               | **Mixed neuroendocrine-nonneuroendocrine neoplasm (MiNEN)** |             |               |

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HPF, high power fields; NEC, neuroendocrine carcinomas; NEN, neuroendocrine neoplasm; NET, neuroendocrine tumours; PanNEN, pancreatic neuroendocrine neoplasm; WHO, world health organisation

KEY CHANGES IN WHO CLASSIFICATION 2017

- Grade 1 to 2 Ki-67 cut-off moved from ≤ 2% to < 3%

- Two groups of patients within G3 category are defined:
  - NET G3 – well differentiated morphology
  - NEC G3 – poorly differentiated morphology

- Naming of mixed cell tumours changed from MANEC to MiNEN

MANEC, mixed adenoneuroendocrine carcinoma; MiNEN, mixed neuroendocrine non-neuroendocrine neoplasms; NEC, neuroendocrine carcinomas; NET, neuroendocrine tumours; WHO, world health organisation

Lloyd, RV et al. WHO Classification of Tumours of Endocrine Organs, IARC Press, Lyon, 2017.
Perren, A. Summary of oral presentation at ENETS 2019
# THERAPEUTIC OPTIONS

**NET G3**
- Somatostatin-based therapy (when receptors expressed)
- Targeted therapies
- Non-platinum-based chemotherapy (i.e. TEMCAP)
- Role of surgery and immunotherapy to be defined

**NEC G3**
- Platinum-based chemotherapy
- Second-line therapy to be defined
- Role of surgery and immunotherapy to be defined

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**Morphology is not the only important feature!**

- **NET G3 with very high Ki-67:**
  - may benefit from platinum-based chemotherapy
- **NEC G3 with not very high Ki-67:**
  - other options such as NET G3 (e.g. TEMCAP or targeted therapies)

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NEC, neuroendocrine carcinomas; NET, neuroendocrine tumours; TEMCAP, Temozolomide-Capecitabine chemotherapy.
SUMMARY

• Previously defined G3 group divided based on tumour morphology into NET G3 and NEC G3

• Anticipate that future updates will propose a similar classification also for other tumour primary sites. Waiting for the new WHO classification for other digestive NENs to be released
  – expected April 2019
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