MEETING SUMMARY
ENETS 2020
VIRTUAL MEETING

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March 2020
NET CONNECT

is supported by an Independent Educational Grant from Ipsen

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DISCLOSURES DR. CIVES

Speaker fees from Ipsen and Novartis
PRESIDENTIAL ABSTRACT

BASIC SCIENCE:

ORGANOID MODELS OF NEUROENDOCRINE CELL GROWTH AND TUMORIGENESIS

• **There are few models** that can be used for mechanistic and drug response studies for neuroendocrine neoplasms (NENs)

• **Advantages of organoids:**
  – Defined in vitro system
  – Can be grown from both healthy and diseased tissues
  – Recapitulate stem cell differentiation dynamics

• **This research aimed to build a NEN biobank of pancreatic, intestinal and lung NECs and NETs**
  – To be used to study normal neuroendocrine cells and model their transformation to NENs
  – Generating pulmonary neuroendocrine cell enriched human airway organoids for characterization and modelling of lung NENs

NEC, neuroendocrine carcinomas; NET, neuroendocrine tumours
Dayton T, et al. ENETS 2020. Abstract #B01 (oral presentation)
SUCCESS RATE IN GENERATING ORGANOIDs

- Success rate in generating organoids higher in lung NENs (87%) as compared with intestinal (56%) or pancreatic NENs (16%)

IntNENs, intestinal neuroendocrine neoplasm; NEC, neuroendocrine carcinoma; NEN, neuroendocrine neoplasm; PaNENs, pancreatic neuroendocrine neoplasm

Dayton T, et al. ENETS 2020. Abstract #B01 (oral presentation)
NEN ORGANOIDS EXPRESS NE MARKERS

**KEY RESULTS**

NEN organoids express NE markers

Lung NENs | Int NENs | PaNENs

CHGA, chromogranin A; EEC, enteroendocrine cell; INSM1, insulinoma-associated 1; IntNENs, intestinal neuroendocrine neoplasm; LCNEC, large cell neuroendocrine carcinoma; NE, neuroendocrine; NEN, neuroendocrine neoplasm; NEUROD1; neurogenic differentiation factor 1; NET, neuroendocrine tumours; PaNEN (pNEN), pancreatic neuroendocrine neoplasm

Dayton T, et al. ENETS 2020. Abstract #B01 (oral presentation)
• Media components critically influence NEN organoid growth
  – Suggests potential therapeutic vulnerabilities
• NEN organoids maintain expression of neuroendocrine markers across multiple passages
• NEN organoids maintain the intratumour heterogeneity of the primary tumour
• NEN organoids allow phylogenetic dissection of tumour sub-clones
• Pulmonary neuroendocrine cell differentiation can be achieved in organoids

NEN, neuroendocrine neoplasm
Dayton T, et al. ENETS 2020. Abstract #B01 (oral presentation)
SUMMARY

- **NEN organoids** and PNEC-enriched fetal AOs are novel preclinical in vitro models for the study of NE biology and disease

- A collection of organoid cultures from NEN primary tumours and matched normal tissue has been established

- The expression of NE markers and the presence of the same genetic alterations identified in the primary tumour suggest that organoids may serve as a bona fide model of NENs

- PNECs are maintained long term over multiple passages and high numbers of differentiated PNEC can be achieved

- PNEC differentiation can be promoted by using a specific cocktail of small molecules
MUTATIONAL LANDSCAPE OF 109 HIGH-GRADE GASTROENTEROPANCREATIC NEUROENDOCRINE NEOPLASMS G3

**BACKGROUND**

- Gastroenteropancreatic (GEP) G3 NENs are rare with a poor outcome
- The genetic background of G3 NENs (NETs + NECs) has been **poorly investigated to date**
- The aim of this research was to gain tools for better prediction and to aid treatment decisions to improve survival in this patient population
- The genetic landscape of **109 high-grade GEP NEN patients (16 NET G3 and 93 NEC)** was assessed from the **Nordic Prospective Registry** between 2013–2017
- DNA from FFPE samples and matched blood samples was analysed
  - All cases were re-assessed by a pathology expert
- NGS targeted sequencing using a pan-cancer panel was used

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DNA, deoxyribonucleic acid; FFPE, formalin-fixed paraffin-embedded; G3, grade 3; NEC, neuroendocrine carcinoma; NEN, neuroendocrine neoplasm; NET, neuroendocrine tumour; NGS, next generation sequencing

### G3, grade 3; NEC, neuroendocrine carcinomas; NET, neuroendocrine tumours


#### NEC

<table>
<thead>
<tr>
<th>Frequently mutated genes</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>TP53</td>
<td>59%</td>
</tr>
<tr>
<td>APC</td>
<td>31%</td>
</tr>
<tr>
<td>BRAF</td>
<td>24%</td>
</tr>
<tr>
<td>KRAS</td>
<td>24%</td>
</tr>
</tbody>
</table>

**Stratified by tumour site**

<table>
<thead>
<tr>
<th>Tumour Site</th>
<th>TP53</th>
<th>BRAF</th>
<th>APC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon (n=31)</td>
<td>68%</td>
<td>52%</td>
<td>42%</td>
</tr>
<tr>
<td>Rectal (n=24)</td>
<td>50%</td>
<td>50%</td>
<td>25%</td>
</tr>
</tbody>
</table>

#### NET G3

<table>
<thead>
<tr>
<th>Frequently mutated genes</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ATRX</td>
<td>19%</td>
</tr>
<tr>
<td>SF3B1</td>
<td>19%</td>
</tr>
<tr>
<td>MEN1</td>
<td>12%</td>
</tr>
</tbody>
</table>

- In remaining tumours (pancreatic, oesophageal, gastric) TP53 was mutated >50%
  - Less frequently mutated genes included DICER, EGFR, FOXO1 and SOX9
• NEC are altered in 87.1% of cases
  – Most common mutations include TP53, APC, BRAF, and KRAS
  – MSI detected in 9% of cases
  – Colon NEC are enriched in mutations of BRAF

• NET G3 are altered in 68.75% of cases
  – Most common mutations include ATRX, SFB1, MEN1

• NET G3 and NEC have distinct genetic features

• This may pave the way to more personalized treatments in the future
INTERIM ANALYSIS OF PROSPECTIVE EVALUATION OF THE MANAGEMENT OF SPORADIC NON-FUNCTIONING ASYMPTOMATIC PANCREATIC NEUROENDOCRINE NEOPLASMS ≤2 CM (ASPEN STUDY)

In the last decade a dramatic increase in diagnosis of small, incidentally discovered, NF-PanNENs was observed.

A relationship between the tumour diameter and low risk of malignancy and systemic progression has been noted:
- A tumour size ≤2 cm seems to be associated with a negligible risk of disease recurrence and with a very low incidence of aggressive features such as lymph node involvement.

Guidance regarding most appropriate management of sporadic asymptomatic NF-PanNETs varies in current guidelines:
- **ENETS**: ‘In patients with... p-NETs ≤2 cm or with NF-pNETs on imaging studies, routine surgical exploration continues not to be generally recommended. In patients with p-NETs>2 cm, enucleation at surgery remains the generally recommended surgical procedure’
- **NANETS**: ‘...initial observation is an acceptable treatment strategy for asymptomatic patients with PanNET <1 cm (...) it is recommended that decision to observe or resect an asymptomatic PanNET 1 to 2 cm in size be individualized’

Available data are based on retrospective studies with a significant heterogeneity of inclusion criteria and different tumour diameter cut-off and the appropriate management. The ASPEN study investigated most appropriate management prospectively.

**BACKGROUND**

ENETS, European Neuroendocrine Tumour Society; NANETS, North America Neuroendocrine Tumour Society; NF, non-functioning; PanNET, pancreatic neuroendocrine tumour.

Prospective international multicenter cohort study
Target enrolment: 1000 patients
Study duration: 6 years (2017-2023)
43 centres involved, including 20 ENETS CoE

Primary objectives:
• To evaluate the most appropriate management (active surveillance versus surgery) of sporadic asymptomatic NF-PanNET ≤2 cm

Secondary objectives:
• To estimate the frequency of asymptomatic sporadic NF-PanNET ≤2 cm among overall sporadic NF-PanNET
• To observe NF-PanNET evolution (development of symptoms, tumour growth, development of distant metastases)
• To evaluate the perceived burden of surveillance or follow-up after surgery for participants

CoE, centres of excellence; ENETS, European Neuroendocrine Tumor Society; FNA, fine needle aspiration; ⁶⁸Ga, gallium-68; NF, non-functioning; PanNET, pancreatic neuroendocrine tumour; PET, positron emission tomography
KEY RESULTS

RESULTS

<table>
<thead>
<tr>
<th></th>
<th>Surveillance n=310</th>
<th>Surgery n=76</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR)</td>
<td>65 (56-72)</td>
<td>58 (51-68)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Diameter, mean (SD)</td>
<td>12.9 (3.9)</td>
<td>14.5 (4.4)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Site lesion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head</td>
<td>83 (26.8)</td>
<td>15 (19.7)</td>
<td>0.08</td>
</tr>
<tr>
<td>Uncinate process</td>
<td>36 (11.6)</td>
<td>7 (9.2)</td>
<td></td>
</tr>
<tr>
<td>Body</td>
<td>107 (34.5)</td>
<td>22 (28.9)</td>
<td></td>
</tr>
<tr>
<td>Tail</td>
<td>84 (27.1)</td>
<td>32 (42.2)</td>
<td></td>
</tr>
<tr>
<td>MPD (mm), mean (SD)</td>
<td>2.4 (3.0)</td>
<td>4.3 (3.8)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>ECOG</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>268 (86.5)</td>
<td>71 (93.4)</td>
<td>0.45</td>
</tr>
<tr>
<td>1</td>
<td>34 (11.0)</td>
<td>5 (6.6)</td>
<td></td>
</tr>
<tr>
<td>≥2</td>
<td>7 (2.5)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Liver metastases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0</td>
<td>2 (0.2)</td>
<td>1</td>
</tr>
<tr>
<td>Ki67 mean (SD)</td>
<td>1.4</td>
<td>2.4</td>
<td>0.01</td>
</tr>
</tbody>
</table>

SURGICAL OUTCOMES

<table>
<thead>
<tr>
<th>Variable</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Resection type</strong></td>
<td></td>
</tr>
<tr>
<td>Pancreaticoduodenectomy</td>
<td>15 (19.7)</td>
</tr>
<tr>
<td>Central pancreatomy</td>
<td>2 (2.6)</td>
</tr>
<tr>
<td>Distal pancreatomy</td>
<td>39 (51.3)</td>
</tr>
<tr>
<td>Enucleation</td>
<td>13 (17.1)</td>
</tr>
<tr>
<td>Other</td>
<td>7 (9.2)</td>
</tr>
<tr>
<td><strong>Surgical approach</strong></td>
<td></td>
</tr>
<tr>
<td>Minimally invasive</td>
<td>46 (60.5)</td>
</tr>
<tr>
<td>Laparotomy</td>
<td>30 (39.5)</td>
</tr>
<tr>
<td><strong>Complication grade</strong></td>
<td></td>
</tr>
<tr>
<td>No complication</td>
<td>52 (68.4)</td>
</tr>
<tr>
<td>I</td>
<td>8 (10.5)</td>
</tr>
<tr>
<td>II</td>
<td>7 (9.2)</td>
</tr>
<tr>
<td>III</td>
<td>5 (6.6)</td>
</tr>
<tr>
<td>IV</td>
<td>4 (5.3)</td>
</tr>
</tbody>
</table>

• Indications for surgery:
  – Patient’s preference: 46%
  – Physician’s preference: 35%
  – Presence of dilation of the main pancreatic duct: 13%
  – Increase in tumour size: 4%
  – Presence of distant metastases: 3%

ECOG, Eastern Cooperative Oncology Group; IQR, inter-quartile range; MPD, main pancreatic duct; SD, standard deviation
SUMMARY

- A large majority of patients with asymptomatic NF-PanNET ≤2 cm undergo active surveillance but a fraction undergo surgery despite guideline recommendations.

- The risk of malignant behaviour for asymptomatic NF-PanNET ≤2 cm exists although very low.

- The main indication for surgery is still related to patient’s preference who cannot cope with a surveillance strategy.

- Tumour size and patient’s age influence physician’s strategy.

- We await the full results of the ASPEN trial.

NF, non-functioning; PanNET, pancreatic neuroendocrine tumour
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