The Unique Biology of Neuroendocrine Tumors of the GI Tract Has Set the Field for Molecular Diagnosis & Targeted Therapies

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Disclosures:

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General considerations

• NETs of the digestive tract are rare diseases

• Pancreatic NET and other NETs of the digestive tract behave differently

• The course of the disease may be indolent for several years

• The lack of specific symptoms is associated with a delayed diagnosis

• Most patients are diagnosed at late stages with bulky tumor masses and metastases (predominantly in the liver)

• Differentiation and proliferation are pathological characteristics that predict the clinical behavior of NET
# Somatic mutations in pancreatic NET

<table>
<thead>
<tr>
<th>Gene</th>
<th>Frequency</th>
<th>Pathway</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MEN1</strong></td>
<td>30–44%¹,²</td>
<td>PI3K/AKT/mTOR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chromatin remodelling</td>
</tr>
<tr>
<td><strong>DAXX/ATRX</strong></td>
<td>43%²</td>
<td>Chromatin remodelling</td>
</tr>
<tr>
<td><strong>TSC2</strong></td>
<td>9%²</td>
<td></td>
</tr>
<tr>
<td><strong>PTEN</strong></td>
<td>7%²</td>
<td>PI3K/AKT/mTOR</td>
</tr>
<tr>
<td><strong>PIK3CA</strong></td>
<td>1%²</td>
<td></td>
</tr>
<tr>
<td><strong>ATM</strong></td>
<td>6%³</td>
<td>ATM/p53 pathway</td>
</tr>
</tbody>
</table>

DAXX, death-domain associated protein; ATRX, alpha thalassemia/mental retardation syndrome X-linked; ATM, ataxia telangiectasia-mutated

NET are highly angiogenic tumors
Well Differentiated NET Are Highly Angiogenic and HIF1-alpha dependent

Couvelard A et al., Br J Cancer. 2005
HIF-1 activation plays an important role in the activation of mTOR and angiogenesis

- Genetic and epigenetic alteration of \( VHL \) in ~30% of sporadic pNET
- Biallelic inactivation of \( VHL \) in familial pNET (von Hippel-Lindau disease)

- Spontaneous area of necrosis in bulky tumors
- Intratumor alterations resulting from treatment with VEGFR inhibitors

**VHL INACTIVATION**

**HYPOXIA**

HIF-1α Accumulation/Activation

Hypoxia-related proteins
CA-9 & GLUT-1

Canonical signaling pathways linked to VEGF/VEGFR & mTOR

SENSITIVITY to VEGFR and mTOR inhibitors

Alternative signaling pathways linked to FGFs, Ephrins & Angiopoietins

EMT

EVASION / ACQUIRED RESISTANCE to VEGFR and mTOR inhibitors

Targeted Therapies @ NET

**NET angiogenesis**
- Endothelial cells
- Pericytes

**NET cells**
- PDGFR
- IGF1R

**Somatostatin analogues**

**Molecular Imaging & PRRT**
(Peptide Receptor Radio Therapy)

**Targeted Therapies**
- Sunitinib
- Everolimus

**Cell survival** – **Cell proliferation** – **Cell migration** – **Angiogenesis** – **Metastasis**

We may take advantage of molecular characteristics of NET to sequence the use of targeted agents.