Evaluation and Management of Neuroendocrine Tumors

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Neuroendocrine Tumors

- Arise from cells in the diffuse neuroendocrine system
- May pursue more indolent clinical course than other malignancies
- Can secrete peptides leading to symptoms of hormone excess
Epidemiology of NET

- Incidence has increased to 7/100,000
- Increasing incidence likely due to improved awareness, classification, and diagnostic modalities
- Projected prevalence in the US in 2014 was 171,321

Dasari A, et al. JAMA Oncol 2017
Key Features of NET

• Pathologic features
  – Grade
  – Differentiation

• Primary site
  – Pancreatic NET
  – “Carcinoid”: GI, lung, thymus

• Functional (hormone secreting) status
# Neuroendocrine Tumors: Histologic Classification

<table>
<thead>
<tr>
<th>Differentiation</th>
<th>Grade</th>
<th>Mitotic Count</th>
<th>Ki-67 Index</th>
<th>Tumor Type</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well differentiated</td>
<td>Low (G1)</td>
<td>&lt; 2 per 10 HPF</td>
<td>≤ 2%</td>
<td>Typical</td>
<td>Carcinoid morphology, &lt;2 mitoses/2mm², no necrosis</td>
</tr>
<tr>
<td></td>
<td>Intermediate (G2)</td>
<td>2-20 per 10 HPF</td>
<td>3-20%</td>
<td>Atypical</td>
<td>Carcinoid morphology, 2-10 mitoses/2mm², foci of necrosis</td>
</tr>
<tr>
<td>Poorly differentiated</td>
<td>High (G3)</td>
<td>&gt; 20 per 10 HPF</td>
<td>&gt;20%</td>
<td>Large cell carcinoma</td>
<td>&gt;10 mitoses/2mm², necrosis cytology resembling NSCLC, IHC positive for NE/granules</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Small cell carcinoma</td>
<td>Small cell size, scant cytoplasm, nuclei with finely granular chromatin and absent or faint nucleoli, &gt;11 mitoses/2mm², extensive necrosis</td>
</tr>
</tbody>
</table>
Neuroendocrine Tumors: Survival Varies by Tumor Grade

- Higher-grade disease correlates with poor survival
- Intermediate prognosis for G2: more similar to G1 than G3

Dasari A, et al. JAMA Oncol 2017
Features of GEP-NET by Grade

<table>
<thead>
<tr>
<th>Differentiation</th>
<th>Well differentiated</th>
<th>Poorly differentiated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade</td>
<td>G1</td>
<td>G2</td>
</tr>
<tr>
<td>Mitotic count</td>
<td>&lt;2 /10 hpf</td>
<td>2-20/10 hpf</td>
</tr>
<tr>
<td>Ki-67</td>
<td>&lt;3%</td>
<td>3-20%</td>
</tr>
<tr>
<td>Clinical course</td>
<td>Indolent</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Somatostatin receptor expression</td>
<td>Higher</td>
<td>Intermediate</td>
</tr>
<tr>
<td>FDG-PET avid lesions</td>
<td>Lower</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Mutations</td>
<td><em>DAXX/ATRX, MEN-1, mTOR pathway (pNET)</em></td>
<td><em>CDKN1B (SI-NET)</em></td>
</tr>
</tbody>
</table>
NET Classification by Primary Site

- **Foregut**
  - Thymus
  - Lung
  - Esophagus
  - Stomach
  - Prox. Duodenum

- **Midgut**
  - Small intestine
  - Appendix
  - Cecum
  - Ascending colon

- **Hindgut**
  - Distal colon
  - Rectum

- **Pancreas**

- **Unknown**

Kulke and Mayer, NEJM, 2009; Yao, JCO, 2008
# Genomic Landscape of NET

## Primary Site

<table>
<thead>
<tr>
<th>Primary Site</th>
<th>Mutations</th>
<th>Reference</th>
</tr>
</thead>
</table>
| Pancreas       | • *MEN1, DAXX/ATRX, mTOR pathway genes*  
                     Scarpa, *Nature*, 2017 |
NET: Survival Varies by Primary Tumor Site

Median Survival of Distant Stage G1/2 NET, 2000-2012

<table>
<thead>
<tr>
<th>Site</th>
<th>Median Survival (mo)</th>
<th>5-year OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appendix</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Cecum</td>
<td>98</td>
<td>61</td>
</tr>
<tr>
<td>Colon</td>
<td>14</td>
<td>29</td>
</tr>
<tr>
<td>Lung</td>
<td>24</td>
<td>32</td>
</tr>
<tr>
<td>Pancreas</td>
<td>60</td>
<td>50</td>
</tr>
<tr>
<td>Rectum</td>
<td>33</td>
<td>28</td>
</tr>
<tr>
<td>Small Intestine</td>
<td>103</td>
<td>69</td>
</tr>
<tr>
<td>Stomach</td>
<td>29</td>
<td>32</td>
</tr>
</tbody>
</table>

NA = not assessed due to small numbers

Dasari A, et al. *JAMA Oncol* 2017
NET: Presenting Symptoms

Questionnaire Data from 731 pts with NET evaluated at DFCI (2003-10)

Ter-Minassian et al, Endocr Relat Cancer, 2013
## Functional NETs: Clinical Presentation

<table>
<thead>
<tr>
<th>Origin</th>
<th>Organ</th>
<th>Clinical Syndrome</th>
<th>Secretory products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foregut</td>
<td>Thymus</td>
<td>Atypical carcinoid syndrome, cough, wheezing, Cushing’s syndrome</td>
<td>ACTH, Serotonin, Histamine</td>
</tr>
<tr>
<td></td>
<td>Respiratory Tract</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stomach</td>
<td>Flushing, gastrin hypersecretion, Cushing’s syndrome</td>
<td>Histamine, Serotonin, Gastrin</td>
</tr>
<tr>
<td></td>
<td>Duodenum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Midgut</td>
<td>Jejunum</td>
<td>Flushing, Diarrhea</td>
<td>“Carcinoid Syndrome”</td>
</tr>
<tr>
<td></td>
<td>Ileum</td>
<td></td>
<td>Serotonin</td>
</tr>
<tr>
<td></td>
<td>Cecum</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Appendix</td>
<td>Syndrome rare</td>
<td></td>
</tr>
<tr>
<td>Hindgut</td>
<td>Colon</td>
<td>Syndrome rare</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rectum</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Carcinoid Syndrome:
Associated Factors

- Frequency of carcinoid syndrome among patients with NET not well established
  - SEER-Medicare (2000-2011): 19% of patients with NET had at least 2 insurance claims of flushing, diarrhea, CS in the 3 months pre/post diagnosis
  - Carcinoid syndrome more common in women, advanced stage, well-differentiated tumors, small intestine primary

Pancreatic NET: Functional Status

- 60%–70% “non-functioning”
- 30%–40% associated with hormone hypersecretion
- Symptoms defined by hormone secreted

<table>
<thead>
<tr>
<th>Symptoms</th>
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</tr>
</thead>
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<tr>
<td>Gastrinoma</td>
<td>Gastric ulcers, diarrhea</td>
</tr>
<tr>
<td>Glucagonoma</td>
<td>Skin rash (necrolytic migratory erythema), hyperglycemia</td>
</tr>
<tr>
<td>Insulinoma</td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td>VIPoma</td>
<td>Diarrhea, hypokalemia</td>
</tr>
</tbody>
</table>
NET: Evaluation Depends on Primary Tumor Location and Symptoms

**GI Endoscopy**

**Bronchoscopy**

**Imaging**
- Cross-sectional imaging: CT or MRI
- Somatostatin receptor scintigraphy
  - Octreotide scan
  - Ga$^{68}$-dotatate PET/CT
- Cardiac echo (carcinoid syndrome)

**Blood/Urine Tests**
- Chromogranin A
- 24-hr urine 5-HIAA (in GI or lung NET if carcinoid syndrome is suspected)
- Other hormone or biochemical workup, as clinically indicated
Neuroendocrine Tumors: Management Principles

- Resection of localized and limited metastatic disease

- Advanced disease
  - Control of hormone secretion for functional tumors
  - Control of growth of disease
Neuroendocrine Tumors

- GI Tract, Lung, Thymus NET (Carcinoid Tumors)
- Pancreatic NET

Management of carcinoid syndrome

Options for disease control
Carcinoid Syndrome

- Caused by secretion of serotonin and other neuropeptides into systemic circulation
- Manifested by episodic flushing, diarrhea, and eventual right sided valvular heart disease

Heart
- Pulmonic and tricuspid valve thickening
- Stenosis
- Endocardial fibrosis

Gastrointestinal
- Diarrhea
- Cramps
- Nausea
- Vomiting

Skin
- Flushing
Somatostatin Analogs and NET

- Octreotide and Lanreotide
- Bind to somatostatin receptors that are highly expressed by NET (>80%)
- Can improve hormone-mediated symptoms by reducing hormone secretion
Carcinoid Syndrome: Improvement with Octreotide

**Diarrhea**: 43% mean reduction in daily stools through week 24

**Flushing**: 85% mean reduction in daily flushing through week 24

Somatostatin Analogs and NET

• Pooled data of 15 octreotide and lanreotide trials including 481 patients
• Lanreotide and octreotide achieve similar improvement in symptoms and biochemical response

Somatostatin Analogs and NET

• Octreotide: Approved in US for carcinoid syndrome in 1998
  – Short-acting sc and depot IM formulations

• Lanreotide: Approved in US for carcinoid syndrome in 2017
  – Depot deep sc formulation
Carcinoid Syndrome: Targeting Serotonin Synthesis

- Treatment with somatostatin analogs (SSAs) is associated with improved symptom control, but patients may not maintain adequate control of symptoms.

- Telotristat etiprate is an oral inhibitor of TPH, the rate-limiting enzyme in serotonin biosynthesis.

TELESTAR: Telotristat vs. Placebo in Patients with Refractory Carcinoid Syndrome

3- to 4-week run-in (n=135)

Run in:
Evaluation of bowel movement (BM) frequency

1:1:1

Placebo TID (n=45)

Telotristat etiprate 250 mg TID (n=45)

Telotristat etiprate 500 mg TID* (n=45)

Telotristat etiprate 500 mg TID

Evaluation of primary endpoint:
Reduction in number of daily BMs from baseline (averaged over 12-week double-blind treatment phase)

All patients required to be on SSA at enrollment and continue SSA therapy throughout study period

Kulke et al, J Clin Oncol 2017
TELESTAR: Reduction in Daily Bowel Movement Frequency Averaged Over Double-Blind Treatment Phase

- Hodges–Lehmann estimator of treatment differences estimated a reduction versus placebo of
  - $-0.81$ BMs daily for telotristat etiprate 250 mg dose ($P<0.001$)
  - $-0.69$ for telotristat etiprate 500 mg dose ($P<0.001$)

Kulke et al, J Clin Oncol 2017
Wilcoxon rank-sum test showed significant differences for each telotristat etiprate dose vs. placebo (p<0.001).

TELESTAR: Mean Absolute Change in Urinary 5-HIAA (mg/24 h) from Baseline to Week 12

- Placebo: n=29 (change: 11.47 mg/24 h)
- Telotristat etiprate 250 mg: n=32 (change: -40.13 mg/24 h)
- Telotristat etiprate 500 mg: n=31 (change: -57.73 mg/24 h)

All patients continue SSA therapy throughout study period. Data include only patients for whom both baseline and Week 12 assessments were available.

Wilcoxon rank-sum test showed significant differences for each telotristat etiprate dose vs. placebo (p<0.001)

5-HIAA, 5-hydroxyindoleacetic acid; SSA, somatostatin analog.
Refractory Carcinoid Syndrome

• Add telotristat to somatostatin analog
• Add therapy to achieve better disease control
  - Liver directed therapy (embolization)
  - Targeted therapy?
    • Everolimus: ↓ urinary 5-HIAA, but symptom control not reported
Antiproliferative Mechanisms of Somatostatin Analogs

Systemic effects

Somatostatin Analogs

Binding to somatostatin receptor on tumor cells

- Inhibition of growth factor signaling
  - Inhibit cell cycle
  - Inhibit growth factor effects
  - Pro-apoptotic effects

Indirect antitumor effect

- ↓ angiogenesis
- Modulation of immune system
- ↓ release of growth factors and trophic hormones

Adapted from Susini & Buscail. *Ann Oncol*, 2006
PROMID: Octreotide LAR vs Placebo in Metastatic Neuroendocrine Midgut Tumors

Locally inoperable or metastatic well differentiated midgut NET

Octreotide LAR
30 mg IM q 4 weeks
(n= 42)

Placebo
(n= 43)

Primary Endpoint
Time to Progression

Rinke et al, JCO, 2009
CLARINET: Lanreotide vs Placebo in Metastatic Enteropancreatic Neuroendocrine Tumors

Non-functional advanced GI or pancreatic NET with positive octreotide scan
- Ki67<10%
- 45% pNET; 36% midgut
- 96% with stable disease at entry

Primary Endpoint
Progression-Free Survival

Lanreotide autogel
120 mg sc q 4 weeks
n= 101

Placebo
n= 103

Caplin, NEJM, 2014
**SPINET Study:**
Lanreotide vs. Placebo for Lung NET

Well-differentiated locally advanced or metastatic lung NET (n=216)

- Typical or atypical carcinoid (WHO)
- Positive octreotide scan

**Lanreotide autogel**
120 mg sc q 4 weeks

**Primary Endpoint**
Progression-Free Survival (central review)

**2° Endpoints:** PFS (local review), TTF, Chromogranin and 24 hr urine 5-HIAA response, Disease Control Rate, ORR, OS, PK, Safety

Open Label Extension for placebo arm at progression and lanreotide arm at data-cutoff
mTOR Biology and NET

- PI3K/AKT/mTOR pathway is a key oncogenic signaling pathway in NET
- Activation of mTOR pathway via IGF-1 is implicated in proliferation of NET
- Downregulation of TSC2 and PTEN in sporadic pancreatic NET leads to activation of mTOR pathway

RADIANT-2: Everolimus + Octreotide LAR in Advanced NET with Carcinoid Syndrome

Progressive, locally advanced or metastatic low- to intermediate-grade NET

1:1

Everolimus + Octreotide LAR
N=216

Placebo + Octreotide LAR
N=213

Primary Endpoint
Progression-Free Survival

Open label extension phase: Option to receive open-label everolimus

- Patients with carcinoid syndrome (regardless of the site of primary tumor)
- Progressive disease within 12 months
- G1-2 tumors

Pavel et al, Lancet, 2011
RADIANT-2: PFS Results

**Central Radiology Review**

<table>
<thead>
<tr>
<th></th>
<th>Everolimus</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS</td>
<td>16.4 mo</td>
<td>11.3 mo</td>
</tr>
<tr>
<td>HR</td>
<td>0.77 (0.59-1.00)</td>
<td></td>
</tr>
</tbody>
</table>

* p-value 0.026 did not meet pre-defined level of significance (p≤0.0246)

**Investigator Radiology Review**

<table>
<thead>
<tr>
<th></th>
<th>Everolimus</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS</td>
<td>12.0 mo</td>
<td>8.6 mo</td>
</tr>
<tr>
<td>HR</td>
<td>0.78 (0.62-0.98)</td>
<td></td>
</tr>
</tbody>
</table>

Pavel et al, Lancet, 2011
RADIANT-4: Everolimus in Advanced Nonfunctional Lung and GI NET

Patients with well-differentiated (G1/G2), advanced, progressive, nonfunctional NET of lung or GI origin (N = 302)
- Absence of active or any history of carcinoid syndrome
- Pathologically confirmed advanced disease
- Enrolled within 6 months from radiologic progression

Randomize

Everolimus 10 mg po daily
N=205

Placebo
N=97

1° Endpoint: PFS

Stratified by:
- Prior SSA treatment (yes vs. no)
- Tumor origin (stratum A vs. B)*
- WHO PS (0 vs. 1)

*Based on prognostic level, grouped as: **Stratum A (better prognosis)** – appendix, caecum, jejunum, ileum, duodenum, and NET of unknown primary. **Stratum B (worse prognosis)** – lung, stomach, rectum, and colon except caecum. Crossover to open label everolimus after progression in the placebo arm was not allowed prior to the primary analysis.

52% reduction in the relative risk of progression or death with everolimus vs placebo

HR = 0.48 (95% CI, 0.35-0.67); P < 0.00001

Kaplan-Meier medians

Everolimus: 11.0 months (95% CI, 9.23-13.31)
Placebo: 3.9 months (95% CI, 3.58-7.43)

P-value is obtained from the stratified one-sided log-rank test; Hazard ratio is obtained from stratified Cox model.
RADIANT-4: Subgroup Analyses by Primary Tumor Location

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>Patients (n)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>90</td>
<td>0.50 (0.28–0.88)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>175</td>
<td>0.56 (0.37–0.84)</td>
</tr>
<tr>
<td>Neuroendocrine tumour of unknown primary origin</td>
<td>36</td>
<td>0.60 (0.24–1.51)</td>
</tr>
</tbody>
</table>

Yao et al, Lancet, 2016
Peptide Receptor Radionuclide Therapy (PRRT)

- Radiolabeled somatostatin analogs
  - Consist of SSTa + chelator + radionuclide
  - $^{111}$In: Auger electrons
  - $^{90}$Y: $\beta$-radiation
  - $^{177}$Lu: $\beta$ and $\gamma$-radiation

- Can deliver tumoricidal doses of radiation to SSTR positive tumors
# PRRT for NET

## Table 2. Tumor responses in GEPNET patients treated with different radiolabeled somatostatin analogs

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Tumor response</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>CR+PR %</td>
<td>Patient, n</td>
<td>CR (%)</td>
<td>PR (%)</td>
<td>MR (%)</td>
<td>SD (%)</td>
<td>PD (%)</td>
<td></td>
</tr>
<tr>
<td><strong>In-octreotide</strong></td>
<td></td>
<td>0</td>
<td>26 [8]</td>
<td>0</td>
<td>0</td>
<td>2 (8)</td>
<td>15 (58)</td>
<td>9 (35)</td>
<td></td>
</tr>
<tr>
<td><strong>In-octreotide</strong></td>
<td></td>
<td>8</td>
<td>26 [9]</td>
<td>0</td>
<td>2 (8)</td>
<td>NA</td>
<td>21 (81)</td>
<td>3 (12)</td>
<td></td>
</tr>
<tr>
<td><strong>90Y-DOTATOC</strong></td>
<td></td>
<td>29</td>
<td>21 [12]</td>
<td>0</td>
<td>6 (29)</td>
<td>NA</td>
<td>11 (52)</td>
<td>4 (19)</td>
<td></td>
</tr>
<tr>
<td><strong>90Y-DOTATOC</strong></td>
<td></td>
<td>24</td>
<td>74 [17, 18]</td>
<td>2 (3)</td>
<td>16 (22)</td>
<td>NA</td>
<td>49 (66)</td>
<td>7 (9)</td>
<td></td>
</tr>
<tr>
<td><strong>90Y-DOTATOC</strong></td>
<td></td>
<td>9</td>
<td>58 [13]a</td>
<td>0</td>
<td>5 (9)</td>
<td>7 (12)</td>
<td>29 (50)</td>
<td>14 (24)</td>
<td></td>
</tr>
<tr>
<td><strong>90Y-DOTATOC</strong></td>
<td></td>
<td>4</td>
<td>90 [14]b</td>
<td>0</td>
<td>4 (4)</td>
<td>NA</td>
<td>63 (70)</td>
<td>15 (17)c</td>
<td></td>
</tr>
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<td><strong>90Y-DOTATOC</strong></td>
<td></td>
<td>23</td>
<td>53 [19]</td>
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<td>NA</td>
<td>34 (64)</td>
<td>7 (13)d</td>
<td></td>
</tr>
<tr>
<td><strong>177Lu-DOTATATE</strong></td>
<td></td>
<td>29</td>
<td>310 [23]</td>
<td>5 (2)</td>
<td>86 (28)</td>
<td>51 (16)</td>
<td>107 (35)</td>
<td>61 (20)</td>
<td></td>
</tr>
</tbody>
</table>

**ORR: 0-30%**

vanVliet et al, Neuroendocrinology, 2013
### Table 2. Tumor responses in GEPNET patients treated with different radiolabeled somatostatin analogs

<table>
<thead>
<tr>
<th>Ligand</th>
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<th>Patient, n [ref.]</th>
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<th>MR (%)</th>
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<th>PD (%)</th>
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<tbody>
<tr>
<td><strong>111In-octreotide</strong></td>
<td>0</td>
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</tbody>
</table>

**90Y-DOTATOC**: More than half who were symptomatic at baseline had durable improvement in symptoms

vanVliet et al, Neuroendocrinology, 2013
NETTER-1: Phase III Study of $^{177}$Lu-Dotatate vs. High Dose Octreotide LAR

Progressive, advanced SSTR+ midgut carcinoid tumors

- Radiographic progression on 20-30 mg octreotide LAR every 3-4 wks within 3 yrs
- Low-intermediate grade disease

1° Endpoint: PFS

Strosberg et al, NEJM 2017
NETTER-1: Progression-Free Survival

HR 0.21 (95% CI, 0.13-0.33)

Strosberg et al, *NEJM* 2017
# NETTER-1: Tumor Response

<table>
<thead>
<tr>
<th></th>
<th>177Lu-Dotatate (n=101)</th>
<th>Octreotide LAR 60mg (n=100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response (n)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Partial Response (n)</td>
<td>17</td>
<td>3</td>
</tr>
<tr>
<td>Objective RR</td>
<td><strong>18%</strong></td>
<td><strong>3%</strong></td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>5%</td>
<td>27%</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>77%</td>
<td>70%</td>
</tr>
</tbody>
</table>

Strosberg et al, *NEJM* 2017
Strosberg et al, ASCO 2016
NETTER-1: Interim Overall Survival

HR 0.40

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>116</th>
<th>108</th>
<th>96</th>
<th>79</th>
<th>64</th>
<th>47</th>
<th>31</th>
<th>21</th>
<th>8</th>
<th>3</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>177Lu-DOTATATE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control group</td>
<td>113</td>
<td>103</td>
<td>83</td>
<td>64</td>
<td>41</td>
<td>32</td>
<td>17</td>
<td>5</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Strosberg et al, NEJM 2017
# NETTER -1: Adverse Events – All grades and Grades 3-4

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Preferred Term</th>
<th>Lutathera (N=111)</th>
<th>Octreotide LAR (N=110)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All grades</td>
<td>Grade 3-4</td>
<td>All grades</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>59%</td>
<td>4%</td>
<td>12%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>47%</td>
<td>7%</td>
<td>10%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>29%</td>
<td>3%</td>
<td>19%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>26%</td>
<td>3%</td>
<td>26%</td>
</tr>
<tr>
<td>Abdominal distension</td>
<td>13%</td>
<td>0%</td>
<td>14%</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue / asthenia</td>
<td>40%</td>
<td>2%</td>
<td>25%</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>14%</td>
<td>0%</td>
<td>7%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>25%</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>18%</td>
<td>9%</td>
<td>2%</td>
</tr>
<tr>
<td>Anemia</td>
<td>14%</td>
<td>0%</td>
<td>5%</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>10%</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>5%</td>
<td>1%</td>
<td>1%</td>
</tr>
</tbody>
</table>

Strosberg et al, *NEJM* 2017
Advanced Carcinoid: Options for Tumor Control

Observation
stable, low volume, no sx

Somatostatin Analog
- GI NET
- Lung?

Progressive Disease

• Regional Therapy
  (Hepatic Artery Embolization)

• Everolimus: GI, lung

• PRRT (awaiting FDA approval)

• Investigational Agents*

• Cytotoxic chemotherapy
  (foregut)?*

Surgery for resectable disease
Neuroendocrine Tumors

GI Tract, Lung, Thymus NET (Carcinoid Tumors)

Pancreatic NET

Options for hormone control
Options for disease control
Pancreatic NET: Management of Secretory Symptoms

- **Glucagonoma**: Somatostatin analog, consider TPN
- **VIPoma**: Somatostatin analog
- **Gastrinoma**: PPIs, +/- somatostatin analog
- **Insulinoma**: Diet modifications, diazoxide, everolimus, +/- somatostatin analog
mTOR Inhibition in Insulinoma

Fiebrich, *Oncologist*, 2011
CLARINET: Lanreotide vs Placebo in Metastatic Enteropancreatic Neuroendocrine Tumors

Non-functional advanced GI or pancreatic NET with positive octreotide scan

- Ki67 < 10%
- 45% pNET; 36% midgut
- 96% with stable disease at entry

Primary Endpoint
Progression-Free Survival

Lanreotide autogel
120 mg sc q 4 weeks
n= 101

Placebo
n= 103

Caplin, NEJM, 2014
CLARINET: Subgroup analysis by primary site

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Patients</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>204</td>
<td>0.47 (0.30–0.73)</td>
</tr>
<tr>
<td>Tumor origin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Midgut</td>
<td>73</td>
<td>0.35 (0.16–0.80)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>91</td>
<td>0.58 (0.32–1.04)</td>
</tr>
<tr>
<td>Hindgut</td>
<td>14</td>
<td>1.47 (0.16–13.24)</td>
</tr>
<tr>
<td>Other or unknown</td>
<td>26</td>
<td>0.21 (0.04–1.03)</td>
</tr>
<tr>
<td>Tumor grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>141</td>
<td>0.43 (0.25–0.74)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>61</td>
<td>0.45 (0.22–0.91)</td>
</tr>
<tr>
<td>Hepatic tumor volume</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤25%</td>
<td>137</td>
<td>0.34 (0.18–0.62)</td>
</tr>
<tr>
<td>&gt;25%</td>
<td>67</td>
<td>0.45 (0.23–0.88)</td>
</tr>
</tbody>
</table>

RADIANT-3: Everolimus for Panc NET

Key Eligibility:
• Low to Intermed Grade Pancreatic NET
• Disease progression in prior 12 mo.

Everolimus 10mg daily (n=207)
Placebo (n=203)

* Concurrent somatostatin analogs allowed (40%)

Option for open-label extension at progression

Progression-free Survival, Local Assessment

- Everolimus 11.0 mo
- Placebo 4.6 mo
- HR 0.35, p<0.001

Updated OS, 2014
- Everolimus 44.0 mo
- Placebo 37.7 mo
- HR 0.94, p=0.3

Yao, NEJM, 2011; Yao, ESMO 2014
Targeting the VEGF Pathway in Neuroendocrine Tumors

- NET are highly vascular
- VEGF and VEGFR overexpression has been observed in both pancreatic NET and carcinoid

Bevacizumab

Vonlizumab

Sunitinib, Sorafenib, Pazopanib

Angiogenesis and Tumor Growth
Sunitinib: Pancreatic NET

Key Eligibility:
- Well-Differentiated Pancreatic NET
- Disease progression in prior 12 mo.

Sunitinib 37.5 mg daily (n=86)
Placebo (n=85)

Option for open-label extension at progression

Sunitinib 11.4 mo
Placebo 5.5 mo
HR 0.42, p<0.001

Updated OS, 2012
- Sunitinib 33 mo
- Placebo 27 mo
HR 0.71, p=0.115

Raymond, NEJM, 2011; Vinik, ASCO, 2012
# Targeted Therapy for Panc NET

<table>
<thead>
<tr>
<th>Sunitinib(^1)</th>
<th>Everolimus(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. of patients treated</strong></td>
<td>86</td>
</tr>
<tr>
<td><strong>Median PFS (95% CI)</strong></td>
<td>11.4 mo (7.4–19.8) vs. 5.5 mo</td>
</tr>
<tr>
<td><strong>Median OS</strong></td>
<td>Not reached</td>
</tr>
<tr>
<td><strong>Objective response rate</strong></td>
<td>9%</td>
</tr>
<tr>
<td><strong>Stable disease rate</strong></td>
<td>63%</td>
</tr>
<tr>
<td><strong>Specific adverse events</strong></td>
<td>Hypertension (26%) Hand-foot syndrome (23%)</td>
</tr>
</tbody>
</table>

Streptozocin-Based Therapy for Pancreatic NET

- Streptozocin/doxorubicin associated with survival benefit compared to streptozocin/5-FU (2.2 vs. 1.5 years) and response rate of 69%.
- Response rates 30%–40% in retrospective series
- Current use limited by side effect profile and schedule of treatment

Figure 2. Length of Time to Disease Progression, According to Treatment Group.
P < 0.001 for the comparison between doxorubicin plus streptozocin and fluorouracil plus streptozocin; P < 0.001 for the comparison between doxorubicin plus streptozocin and chlorozotocin.

# Temozolomide-Based Therapy in Pancreatic NET

<table>
<thead>
<tr>
<th>Regimen</th>
<th>N</th>
<th>RR</th>
<th>TTP/PFS (mo)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Retrospective Series</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tem</td>
<td>12</td>
<td>8%</td>
<td>NR</td>
<td>Ekeblad, Clin Cancer Res 2007</td>
</tr>
<tr>
<td>Tem/Capecitabine</td>
<td>143</td>
<td>53%</td>
<td>17</td>
<td>Cives, Endocrine Rel Cancer 2016</td>
</tr>
<tr>
<td>Tem (various regimens)</td>
<td>53</td>
<td>34%</td>
<td>13.6</td>
<td>Kulke, Clin Cancer Res 2009</td>
</tr>
<tr>
<td><strong>Prospective Trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tem/Thalidomide</td>
<td>11</td>
<td>45%</td>
<td>NR</td>
<td>Kulke, JCO 2006</td>
</tr>
<tr>
<td>Tem/Bevacizumab</td>
<td>15</td>
<td>33%</td>
<td>14.3</td>
<td>Chan, JCO 2012</td>
</tr>
<tr>
<td>Tem/Everolimus</td>
<td>40</td>
<td>40%</td>
<td>15.4</td>
<td>Chan, Cancer 2013</td>
</tr>
</tbody>
</table>

RR 33%–70%; PFS 13.6–17 mo
Tem + Capecitabine: Best Radiographic Response

Strosberg et al., Cancer 2011
Low and intermediate grade advanced pNETs

n=145

CT scans every 3 cycles
Treatment will continue for a max of 13 cycles

ARM A:
Temozolomide 200 mg/m² po QD days 1-5
28 day cycle

ARM B:
Capecitabine 750 mg/m² po BID days 1-14
Temozolomide 200 mg/m² QD days 10-14
28 day cycle

1° Endpoint: PFS
2° Endpoints: RR, OS, toxicity, MGMT
correlative studies
Panc NET: Treatment Approach

- **Observation**: stable, low volume, no sx
- **Somatostatin Analog**
- **Everolimus**
- **Sunitinib**
- **Chemotherapy**: symptoms, high volume
- **Liver-directed Therapy**

- **Surgery for resectable disease**
- **Tumor Control**

**Progressive Disease**
- Investigational Agents
- PRRT*

* Not currently FDA approved
# Neuroendocrine Tumors: Treatment Selection

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Disease-related Factors</th>
<th>Treatment Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Symptomatic vs. asymptomatic</td>
<td>• Low/intermediate vs. high grade</td>
<td>• Shrinkage vs. stabilization of disease</td>
</tr>
<tr>
<td>• Co-morbidities affecting treatment side-effects</td>
<td>• Stable vs. progressive</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Low vs. high volume</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Resectable vs. non-resectable</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Liver predominant vs. widespread metastases</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Functional vs. non-functional tumor</td>
<td></td>
</tr>
</tbody>
</table>
Conclusions

• Multiple options exist to control hormone secretion and growth of NET

• Patient, disease, and treatment characteristics influence treatment choice

• Multidisciplinary approach is critical

• Future studies to identify novel agents and predictors of treatment response are needed