Collaborative Practice in the Management of Patients With Gastrointestinal and Pancreatic Neuroendocrine Tumors
Collaborative Practice in the Management of Patients With Gastrointestinal and Pancreatic Neuroendocrine Tumors

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Financial Disclosure

- Dr. Chan has served as a consultant for Novartis and Ipsen. In addition, she has received institutional research funding from Novartis and Sanofi-Aventis and has stock in Merck.
- Dr. Sommers has served as a consultant for Ipsen and Lexicon.
Learning Objectives

1. Discuss how medical therapies fit within the wider range of treatment options available to patients with gastrointestinal or pancreatic neuroendocrine tumors (pNETs)
2. Define the role of mTOR inhibitors and tyrosine kinase inhibitors in patients with recurrent disease
3. Review the role for somatostatin analogs in patients with both functional and nonfunctional tumors
4. Summarize key references to pivotal clinical trials published in the medical literature
5. Describe best practices for recognizing and managing adverse reactions associated with medical therapy for pNETs
6. Recall key laboratory and imaging studies recommended for patients being treated for pNETs
Multidisciplinary Team Approach

Social Worker

Oncologist

Pathologist

Gastroenterologist

Radiation Oncologist

Nursing

Surgeon

Advanced Practice Clinician

Psychiatry/Psychologist

Palliative Care

Nutritionist

Patient
Additional Specialists

- Radiologists
- Nuclear medicine specialists
- Interventional radiology
- Genetic risk and prevention specialist
- Anesthesiologist
- Pathologists
Resources

- Multidisciplinary new patient clinics
- Tumor board
- Neuroendocrine support group
- Collaborative practice model (MD/advanced practice clinician)
Goals of Advanced Practitioner/Physician Partnerships in Ambulatory Oncology Care

- Improve patient care
- Increase clinical productivity
- Improve access for new patients
- Urgent care
- Coverage for MD
- Care of long-term cancer survivor
Neuroendocrine Tumors

- Arise from cells in the diffuse neuroendocrine system throughout the body
- May pursue a more indolent clinical course than other malignancies
- Can secrete peptides resulting in characteristic syndromes related to hormone secretion
NET: Incidence Is Increasing

- Early estimates of incidence 1–2 per 100,000 population
- Increasing incidence likely due to improved awareness, classification, and diagnostic modalities

Key Features of NET

- Pathologic features
  - Grade
  - Differentiation
- Primary site
  - Pancreatic NET
  - “Carcinoid”: GI, lung, thymus
- 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>WHO ENETS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well differentiated</td>
<td>Low (G1)</td>
<td>&lt; 2 per 10 HPF</td>
<td>≤ 2%</td>
<td>Neuroendocrine tumor, grade 1</td>
</tr>
<tr>
<td>Intermediate (G2)</td>
<td></td>
<td>2-20 per 10 HPF</td>
<td>3-20%</td>
<td>Neuroendocrine tumor, grade 2</td>
</tr>
<tr>
<td>Poorly differentiated</td>
<td>High (G3)</td>
<td>&gt; 20 per 10 HPF</td>
<td>&gt;20%</td>
<td>Neuroendocrine carcinoma, grade 3, small cell</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Neuroendocrine carcinoma, grade 3, large cell</td>
</tr>
</tbody>
</table>

NET Grade Correlates With Prognosis

- 285 patients with metastatic pancreatic and midgut NET
- Higher-grade disease correlates with poor survival

Key Features of NET

- Pathologic features
  - Grade
  - Differentiation

- Primary site
  - “Carcinoid”: GI, lung, thymus
  - Pancreatic NET
Metastatic Neuroendocrine Tumors: Survival Varies by Primary Tumor Type

Single Institution Database (N = 677)

- **Pancreatic NET**: 3.9 yr
- **Small-bowel carcinoid**: 7.9 yr

SEER Database

<table>
<thead>
<tr>
<th>Site</th>
<th>Localized</th>
<th>Regional</th>
<th>Distant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appendix</td>
<td>&gt;360</td>
<td>&gt;360</td>
<td>27</td>
</tr>
<tr>
<td>Cecum</td>
<td>135</td>
<td>107</td>
<td>41</td>
</tr>
<tr>
<td>Colon</td>
<td>261</td>
<td>36</td>
<td>5</td>
</tr>
<tr>
<td>Duodenum</td>
<td>107</td>
<td>101</td>
<td>57</td>
</tr>
<tr>
<td>Gastric</td>
<td>154</td>
<td>71</td>
<td>13</td>
</tr>
<tr>
<td>Liver</td>
<td>50</td>
<td>14</td>
<td>12</td>
</tr>
<tr>
<td>Lung</td>
<td>227</td>
<td>154</td>
<td>16</td>
</tr>
<tr>
<td>Pancreas</td>
<td>136</td>
<td>77</td>
<td>24</td>
</tr>
<tr>
<td>Rectum</td>
<td>290</td>
<td>90</td>
<td>22</td>
</tr>
<tr>
<td><strong>Small bowel</strong></td>
<td>111</td>
<td>105</td>
<td>56</td>
</tr>
<tr>
<td>Thymus</td>
<td>110</td>
<td>68</td>
<td>40</td>
</tr>
</tbody>
</table>

Pancreatic NET: 2 yr
Small-bowel carcinoid: 4.6 yr


NET: Differences by Primary Site

- Survival varies by primary tumor site
- Pancreatic NET are more responsive to cytotoxic chemotherapy and targeted agents

Distinct treatment approaches and clinical trials for pancreatic and non-pancreatic NET
Key Features of NET

- Pathologic features
  - Grade
  - Differentiation

- Primary site
  - Pancreas
  - “Carcinoid”: GI, lung, thymus

- Functional (hormone secreting) status
Functional vs. Non-functional NET

- Functional NET: Secrete serotonin and other neuropeptides (histamine, kinins)
- “Carcinoid syndrome” in 10%–20% of small intestine NET
  - Flushing, telangectasia
  - Diarrhea, abdominal pain
  - Wheezing/shortness of breath
  - Palpitations, valvular heart disease

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>
<th></th>
</tr>
</thead>
<tbody>
<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>

Advanced NET: Evaluation Depends on Primary Tumor Location and Symptoms

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

Imaging
- Cross-sectional imaging: CT or MRI
- Octreotide scan
- Cardiac echo (carcinoid syndrome)
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
Case #1

- 58-year-old male presented to the emergency room with chief complaint of abdominal pain
- Imaging studies revealed a mass at the head of the pancreas
- Underwent Whipple procedure
- Pathology reveals well to moderately differentiated 2 cm pancreatic endocrine tumor, no lymphovascular invasion, 7 peripancreatic lymph nodes negative
- Followed closely over the next couple of years with clinical evaluation, labs, and serial scans
Case #1 Continued…

- Surveillance CT scan of abdomen showed multiple hepatic lesions showing mild enhancement concerning for metastatic disease
- CT guided biopsy: Positive for metastatic low grade epithelial neoplasm consistent with primary
- LFTS, insulin c-peptide, and chromogranin A normal
- Octreoscan: Positive tracer uptake in liver
- Asymptomatic at this time
Arterial Phase

Portal Venous Phase

Images courtesy of Dr. Chan
Portal Venous Phase

Octreotidide Scan

Images courtesy of Dr. Chan
Which of the following management options do you recommend?

A. Somatostatin analog  **JL621**
B. Observe, serial scans and marker  **JL622**
C. Hepatic regional therapy  **JL623**
D. Surgery  **JL624**
E. Everolimus or sunitinib  **JL625**
Audience Response Question

Which of the following management options do you recommend?

A. Somatostatin analog
B. Observe, serial scans and marker
C. Hepatic regional therapy
D. Surgery
E. Everolimus or sunitinib
Advanced Pancreatic NET: Options for Disease Control
Somatostatin Analogs and NET

- Bind to SST receptors (sstr 1-5) that are highly expressed by NET (>80%)
- Both octreotide and lanreotide have high affinity for sstr 2,5
- Can improve hormone-mediated symptoms
Octreotide and Lanreotide for Advanced NET

**PROMID Study**

N = 85 pts  
Midgut only  
Grade 1 (Ki67 ≤ 2%)

**CLARINET Study**

N = 204 pts  
Pancreas 45%, midgut 35%, Hindgut 7%, unknown/other 13%  
Grade 1 (Ki67 < 10%)

Potential Somatostatin Analog–Related Conditions

- Glucose regulation disorders
  - Hypoglycemia, hyperglycemia
- Thyroid disorders
- Cardiovascular disorders
- $B_{12}$ deficiency
- Gallbladder disease: Cholelithiasis and gallbladder sludge
mTOR Inhibitors 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
Targeting the VEGF Pathway in NET

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

Angiogenesis and tumor growth
Sunitinib and Everolimus for the Treatment of Pancreatic Neuroendocrine Tumors: Investigator-Assessed PFS


## Targeted Therapy for Pancreatic NET

<table>
<thead>
<tr>
<th></th>
<th>Sunitinib&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Everolimus&lt;sup&gt;2&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients treated</td>
<td>86</td>
<td>207</td>
</tr>
<tr>
<td>Median PFS (95% CI)</td>
<td>11.4 mo (7.4–19.8)</td>
<td>11.0 mo (8.4–13.9)</td>
</tr>
<tr>
<td>vs. placebo arm</td>
<td>vs. 5.5 mo</td>
<td>vs. 4.6 mo</td>
</tr>
<tr>
<td>Median OS</td>
<td>Not reached</td>
<td>Not reached</td>
</tr>
<tr>
<td>Objective response rate</td>
<td>9%</td>
<td>5%</td>
</tr>
<tr>
<td>Stable disease rate</td>
<td>63%</td>
<td>73%</td>
</tr>
<tr>
<td>Specific adverse events</td>
<td>Hypertension (26%)</td>
<td>Pneumonitis (17%)</td>
</tr>
<tr>
<td></td>
<td>Hand-foot syndrome (23%)</td>
<td>Hyperglycemia (13%)</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)
- Response rates 30%–40% in retrospective series


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>
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<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>30</td>
<td>70%</td>
<td>18</td>
<td>Strosberg, Cancer 2011</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>
<tr>
<td>Tem/Capecitabine</td>
<td>11</td>
<td>36%</td>
<td>&gt;20</td>
<td>Fine, ASCO GI 2014</td>
</tr>
</tbody>
</table>

RR 33%–70%; PFS 13.6–18+ mo

*Data shown above limited to panc NET only, although studies may have included both pNET and carcinoid.*
ECOG 2211 Study

Low and intermediate grade advanced pNET

n = 145

Stratify:
Prior everolimus
Prior sunitinib
Concurrent octreotide
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

CALGB 80701: Randomized Phase II Trial
Everolimus vs. Everolimus + Bev in Advanced pNET


<table>
<thead>
<tr>
<th>Arm</th>
<th>N (Events)</th>
<th>Median (95% CI)</th>
<th>HR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Everolimus</td>
<td>75 (57)</td>
<td>14.0</td>
<td>0.80</td>
<td>.12</td>
</tr>
<tr>
<td>Everolimus + Bev</td>
<td>75 (59)</td>
<td>16.7</td>
<td>(0.55-1.17)</td>
<td>.12</td>
</tr>
</tbody>
</table>

CALGB 80701: Progression-Free Survival by Treatment Arm (Investigator-Assessed)
Metastatic NET: Liver-Directed Therapies

Hepatic resection considered for limited hepatic metastases

Hepatic artery embolization considered for patients with liver predominant disease that is not resectable

Images courtesy of Dr. Chan
Case #1 continued...

- Followed closely with clinical evaluations, labs, and imaging studies
- Restaging scans show mild progression of disease within liver, patient experiencing symptoms of fatigue
Audience Response Question

Which of the following management options do you recommend?

A. Initiate somatostatin analog  JL626
B. Sunitinib or everolimus  JL627
C. Chemotherapy  JL628
D. Hepatic artery embolization  JL629
Audience Response Question

Which of the following management options do you recommend?

A. Initiate somatostatin analog
B. Sunitinib or everolimus
C. Chemotherapy
D. Hepatic artery embolization
Case #1 continued...

- Patient initiated on somatostatin analog
- Followed by serial monthly exams, interval imaging and markers
- Restaging scans after 3 years of therapy with somatostatin analog show mild interval increase liver lesions
Audience Response Question

What management options do you recommend?

A. Chemotherapy  JL630
B. Sunitinib or everolimus  JL631
C. Hepatic-directed therapy  JL633
D. Peptide receptor radionuclide therapy  JL634
What management options do you recommend?

A. Chemotherapy
B. Sunitinib or everolimus
C. Hepatic-directed therapy
D. Peptide receptor radionuclide therapy
Case #1 Continued…

- MD reviews potential treatment options, initiates treatment with everolimus following consent and patient education on medication
Safety Issues Surrounding Oral Chemotherapy

- Medication errors
  - “Check and balances”
  - Refills?
  - Pharmacy systems
- Communication errors
  - Side effects and toxicities
  - Monitoring systems
  - Accurate medication history
- Biohazard concerns
  - Lack of standard system

Case #1 Continued…

- Pharmacy contacts patient within 24 hours for follow-up education
- Nurse contacts patient within 72 hours of starting therapy
- Scheduled to see NP in 2-week follow-up visit and toxicity check
- Patient has evidence of grade II mucositis, had stopped therapy 2 days prior to visit; therapy held
Case #1 Continued…

- Patient returns for 2-week follow-up visit
- Mucositis resolved, resumes everolimus with dose reduction 5 mg po daily
- He is doing well on treatment but wonders what other treatment options exist for the future
Case #2

- 54-year-old man with anxiety and hypertension who presents with post-prandial flushing, frequent loose stools, and abdominal discomfort after eating
- He is diagnosed with IBS
- After experiencing months of symptoms, he sees a gastroenterologist and undergoes further testing
Case #2 Continued…

- Abd CT scan: Thickening in the small intestine, bilobar hyperenhancing lesions throughout liver concerning for metastatic disease
- Liver biopsy: Metastatic low grade neuroendocrine tumor
- Octreotide scan: Multiple areas of uptake in the liver
- Chromogranin A: 504 ng/mL (ref ≤ 225)
- 24-hr urine 5-HIAA = 28 mg (normal < 6 mg/24 hr)
- Echocardiogram: normal

Images courtesy of Dr. Robin Sommers
Management of Carcinoid Syndrome
Somatostatin Analogs and NET

- Bind to SST receptors (sstr 1-5) that are highly expressed by NET (>80%)
- Both octreotide and lanreotide have high affinity for sstr 2,5
- Can improve hormone-mediated symptoms
Response to Octreotide in Patients With Carcinoid Syndrome

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

Targeting Serotonin Synthesis

Tryptophan

Tryptophan Hydroxylase (TPH)

Telotristat Etiprate

5-Hydroxytryptophan

5-HIAA
(5-Hydroxyindoleacetic acid)

Serotonin
(5-Hydroxytryptamine, 5-HT)
Telotristat etiprate significantly reduced bowel movement frequency in patients with carcinoid syndrome taking SSAs

Advanced Carcinoid: Options for Disease Control
Advanced Carcinoid: Disease Control

- Regional therapy
- Somatostatin analogs
- Everolimus
- Interferon-\(\alpha\)
- Investigational agents
  - VEGF pathway inhibitors
- Peptide receptor radionuclide therapy (PRRT)
Octreotide and Lanreotide for Advanced NET

**PROMID Study**

- Placebo, 40 events; median, 6.0 months
- Octreotide LAR, 26 events; median, 14.3 months

**CLARINET Study**

- Lanreotide 120 mg 32 events, 101 patients
  - Median not reached
- Placebo 60 events, 103 patients
  - Median, 18.0 mo (95% CI, 12.1–24.0)

N = 85 pts
Midgut only
Grade 1 (Ki67 ≤ 2%)

N = 204 pts
Pancreas 45%, midgut 35%, Hindgut 7%, unknown/other 13%
Grade 1 (Ki67 < 10%)


**mTOR Inhibitors 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 Trial

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

1:1

Everolimus + Octreotide LAR  n = 216

Placebo + Octreotide LAR  n = 213

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

Central radiology review*

12.0 mo  8.6 mo  0.78 (0.62-0.98)

Local radiology review

*Discrepancies between local and central review → informative censoring and loss of events

RADIANT-4 Trial

Progressive, locally advanced, progressive, low- to intermediate-grade nonfunctional lung or GI NET

Randomized 2:1

Everolimus
n = 205

Placebo
n = 97

Endpoints
- **Primary**: PFS (central)
- **Key Secondary**: OS

Yao et al. ESMO 2015
RADIANT-4 Trial: PFS by Central Review
Everolimus Improves PFS in Progressive GI and Lung NET

Yao et al. ESMO 2015
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

Images courtesy of Dr. Robin Sommers
NETTER-1: Phase III Study of 177Lu-DOTA$^0$-Tyr$^3$-Octreotide vs. High-Dose Octreotide

- Progressive, advanced SSTR+ midgut carcinoid tumors
- Radiographic progression on 20–30 mg octreotide LAR every 3-4 wk within 3 yr
- Low-intermediate grade

177 Lu-DOTA0-Tyr$^3$-octreotate every 2 months x 4 + octreotide LAR

Octreotide LAR 60 mg every month

Primary Endpoint: PFS

Ruszniewski et al. ESMO 2015.
NETTER-1: PRRT Improves PFS in Progressive Mid-Gut NET

N = 229 (ITT)
Number of events: 90
- $^{177}$Lu-Dotatate: 23
- Oct 60 mg LAR: 67

Hazard Ratio [95% CI]
0.209 [0.129 – 0.338]
p < 0.0001

$^{177}$Lu-Dotatate
Median PFS: Not reached

Octreotide LAR 60 mg
Median PFS: 8.4 months

Progression free survival (PFS) [months]

All progressions centrally confirmed and independently reviewed for eligibility (SAP)

Presentation Presidential Session II of the 18th ECCO – 40th ESMO – European Cancer Congress 2015, 27 September 2015, abstract 6LBA, Vienna

Ruszniewski et al. ESMO 2015.
Which of the following management options do you recommend?

A. Observe, serial scans and markers  JL634
B. Somatostatin analog therapy  JL635
C. Hepatic artery embolization  JL636
D. Hepatic resection  JL637
E. Everolimus or sunitinib  JL638
Which of the following management options do you recommend?

A. Observe, serial scans and markers
B. Somatostatin analog therapy
C. Hepatic artery embolization
D. Hepatic resection
E. Everolimus or sunitinib
Conclusions

- Multidisciplinary approach is critical
- Somatostatin analogs remain a mainstay in the treatment of functional NET to palliate symptoms related to hormone secretion; novel agents (telotristat) have shown promise in controlling symptoms in patients with refractory carcinoid syndrome
- Multiple options for disease control exist:
  - Hepatic directed therapies for hepatic predominant disease
  - Alkylating agents (streptozocin and temozolomide) in pancreatic NET
  - Sunitinib and everolimus improve PFS in pancreatic NET; everolimus improves PFS in non-functional lung and GI NET
  - PRRT improves PFS in progressive mid-gut NET
  - Clinical trial enrollment is encouraged.
- Collaborative practice models can enhance patient care