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

- Oncologist
- Surgeon
- Advanced Practice Clinician
- Nursing
- Radiation Oncologist
- Gastroenterologist
- Pathologist
- Social Worker
- Palliative Care
- Nutritionist
- Psychiatry/Psychologist

Diagram shows the interconnected roles in a multidisciplinary team approach for patient care.
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
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></td>
<td>Intermediate (G2)</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>
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</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>Small bowel</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

### Symptoms

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Symptoms</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

Octreotide 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
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**

- No. of patients at risk:
  - Placebo: 43
  - Octreotide LAR: 42

- Log-rank test stratified by functional activity: $P = .000072$, HR = 0.34 (95% CI, 0.20 to 0.59)

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

**CLARINET Study**

- No. at Risk:
  - Lanreotide: 101
  - Placebo: 103

- Hazard ratio for progression or death: 0.47 (95% CI, 0.30–0.73)

- 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(^1)</th>
<th>Everolimus(^2)</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>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Retrospective Series</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Tem</td>
<td>12</td>
<td>8%</td>
<td>NR</td>
<td>Ekeblad, <em>Clin Cancer Res</em> 2007</td>
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<tr>
<td>Tem/Capecitabine</td>
<td>30</td>
<td>70%</td>
<td>18</td>
<td>Strosberg, <em>Cancer</em> 2011</td>
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<tr>
<td>Tem (various regimens)</td>
<td>53</td>
<td>34%</td>
<td>13.6</td>
<td>Kulke, <em>Clin Cancer Res</em> 2009</td>
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<tr>
<td><strong>Prospective Trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Tem/Thalidomide</td>
<td>11</td>
<td>45%</td>
<td>NR</td>
<td>Kulke, <em>JCO</em> 2006</td>
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<tr>
<td>Tem/Bevacizumab</td>
<td>15</td>
<td>33%</td>
<td>14.3</td>
<td>Chan, <em>JCO</em> 2012</td>
</tr>
<tr>
<td>Tem/Everolimus</td>
<td>40</td>
<td>40%</td>
<td>15.4</td>
<td>Chan, <em>Cancer</em> 2013</td>
</tr>
<tr>
<td>Tem/Capecitabine</td>
<td>11</td>
<td>36%</td>
<td>&gt;20</td>
<td>Fine, ASCO GI 2014</td>
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</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

**ARM A**
Temozolomide 200 mg/m\(^2\) po QD days 1-5
28-day cycle

**ARM B**
Capecitabine 750 mg/m\(^2\) po BID days 1-14
Temozolomide 200 mg/m\(^2\) QD days 10-14
28-day cycle

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

1° Endpoint: PFS
2° Endpoints: RR, OS, toxicity, MGMT correlative studies

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

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
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
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
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
NCCN Guidelines: Neuroendocrine Tumors of the Pancreas

**MANAGEMENT OF LOCOREGIONAL UNRESECTABLE DISEASE AND/OR DISTANT METASTASES**

- **If complete resection possible:**
  - Resect metastases + primary
  - Clinically significant progressive disease, see below

- **Locoregional unresectable disease and/or Distant metastases**
  - **Asymptomatic, low tumor burden, and stable disease**
    - • Observe with markers and scans every 3–12 mo
    - • Consider treatment with octreotide or lanreotide
    - Clinically significant progressive disease, see below

  - **Symptomatic or Clinically significant tumor burden or Clinically significant progressive disease**
    - Manage clinically significant symptoms as appropriate
    - [PanNET-1, PanNET-2, PanNET-3, PanNET-4, and PanNET-5]
    - Consider octreotide or lanreotide if not already receiving and/or
      • Everolimus (10 mg/d)
      • Sunitinib (37.5 mg/d)
      • Cytotoxic chemotherapy
      • Hepatic regional therapy (ie, arterial embolization, chemoembolization, radioembolization [category 2B])
      • Cytoreductive surgery/ablative therapy (category 2B)

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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 → Serotonin (5-Hydroxytryptamine, 5-HT) → 5-HIAA (5-Hydroxyindoleacetic acid)
TELESTAR: Phase III Study of Telotristat for Refractory Carcinoid Syndrome

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-α
- Investigational agents
  - VEGF pathway inhibitors
- Peptide receptor radionuclide therapy (PRRT)
Octreotide and Lanreotid for Advanced NET

PROMID Study

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

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


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)

P < 0.001 for the comparison of progression-free survival
Hazard ratio for progression or death, 0.47 (95% CI, 0.30–0.73)

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

1:1

**RADIANT-2 Trial**

<table>
<thead>
<tr>
<th>Placebo + Octreotide LAR</th>
<th>n = 213</th>
</tr>
</thead>
<tbody>
<tr>
<td>Everolimus + Octreotide LAR</td>
<td>n = 216</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Everolimus</th>
<th>Placebo</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central radiology review*</td>
<td>16.4 mo</td>
<td>11.3 mo</td>
<td>0.77 (0.59-1.00)</td>
</tr>
<tr>
<td>Local radiology review</td>
<td>12.0 mo</td>
<td>8.6 mo</td>
<td>0.78 (0.62-0.98)</td>
</tr>
</tbody>
</table>

*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

Randomize 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

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

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

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 $^{177}$Lu-DOTA$^0$-Tyr$^3$-Octreotate 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

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

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
Audience Response Question

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

DR. ROBIN SOMMERS: Good afternoon. I hope you’re all enjoying the conference. I certainly am very, very happy to be here. I’ve attended some of the sessions and I’ve found all of them very enlightening. So, Dr. Chan and I are here today to talk to you about a subject that is near and dear to our hearts and is actually a major part of our practice, and that’s caring for patients with pancreatic and carcinoid tumors. So I’d like to start by first saying how many of you out in the audience take care of patients with this diagnosis? Well, this is exciting. This is very exciting. Fourteen years ago when I started at Dana-Farber I probably saw one patient a year in my general oncology practice, and so now, I probably see about 50 a week.

Starting with that, these are just our disclosures today that you can see. These are the learning objectives and these should be all in your app that you’ll be able to download. For those of you that were there yesterday, I talked a little bit in the colon cancer lecture about the role of multi-disciplinary teams. The care of these patients is very, very complicated, and trying to determine what the right treatment option generally is very difficult. In our center where we see a lot of these patients, we have these multi-disciplinary teams. And I know that’s not always available in the community care facilities. Sometimes we’ll get a lot of referrals from community practices, just because of the volume and the treatment options or clinical trials that we may have available for these patients.
At any given time, the patient may see the oncologist or see a surgeon or see an interventional radiologist, because we’re talking about maybe doing a liver-directed therapy. I did not do this intentionally, but certainly, our pharmacists play a very, very major role, too. I didn’t want to eliminate them in the slide today, as I failed to mention it yesterday and I apologize for that.

There are other members of the team that I would have to point out, too: our nuclear medicine specialists, our interventional radiologists, certainly our genetic counselors for those patients that may have MEN1 or MEN2, anesthesiologists, pathologists, radiologists, etc. So being a neuroendocrine kind of center in the New England area, we have a lot of different options that are available for patients. One of those is the neuroendocrine support group, which our patients have found very helpful. That’s a support group that’s run every other month. The first hour of that is didactic or an information piece that the patients are really interested in. It’s a topic that they want to learn about. It may be Dr. Chan or her colleague, Dr. Kulke, or it may be a nutritionist or a psychologist. The patients and their caregivers or loved ones participate in that conference for the first hour. Then they break off. They have a room where the caregivers will go to one area and the patients will go into another room, and that’s their hour of support time.

We have a collaborative practice model at Dana-Farber, and it’s really nice, as we have 23 physicians and 5 nurse practitioners. We all kind of work with a group of physicians, but we cross-cover each other when one of us is out of town. We see patients with more of kind of a shared model, so we alternate
visits, which is really nice. But, our physicians, generally, are on site if they’re not traveling, and certainly, they’re always available for collaborative information if we’re seeing a patient with scan results, etc, that may have some changes.

We have tumor boards, too. So, for some of our more complicated patients, we have a tumor board that runs and the cases are presented. We have pathologists and surgeons and GI specialists and nurses and physician assistants and pharmacists, etc. So everyone’s welcome to attend.

I like to always toot our horn about how wonderful we are. So I talked about this a little bit yesterday, and that was certainly our role as advanced practice clinicians and what we can bring to a practice. I shared this study yesterday that was actually completed by one of the physicians that used to work at Dana-Farber. He really looked at the impact that advanced practice nurses and physician assistants can make in a practice. He found, actually, that we can help improve patient care because the patients have the best of both worlds. They have a part of, certainly, the medical model and the physician model working collaboratively with a nurse practitioner or physician assistant.

We can help increase productivity, especially for those of us that have practices where we may see 14 or 15 patients in a day and the physician’s seeing another group of patients in a day. Most of our patients have indolent disease and, certainly, Dr. Chan will allude to the ones that are poorly differentiated. These patients live a long time and we’re thrilled about that. But, the practice keeps growing and growing and growing. How can we meet the needs and be able to bring new patients in, with this collaborative model? We
see the urgent care patients certainly, again, freeing up our physician colleagues that are involved in other activities involving their research, etc. Certainly, we cover our physicians when they’re out of town. We don’t take call at night in our particular practice model, but we will carry their pagers during the day with a physician colleague that’s a backup, if we should so need them.

And, certainly, we can’t forget about our long-term cancer survivors. There’s actually one of the presentations that I had read about: how we can incorporate that model into our practice. So now I’ll turn the podium over to Dr. Chan.

**DR. JENNIFER CHAN:** Great, thanks. I want to start first by reviewing neuroendocrine tumors, what they are, and what our approach to management is. So as many of you know, neuroendocrine tumors are neoplasms that arise from the diffuse neuroendocrine system, which exists throughout the body. Compared to some of the other malignancies we may see, they often will pursue a more indolent course. And one other very distinguishing feature of these tumors is that they can secrete various peptides, which result in symptoms that are classic and related to the hormones that are being secreted.

Although we typically think of neuroendocrine tumors as a relatively rare malignancy, it’s important also to recognize that the incidence of neuroendocrine tumors is increasing. Previously, some of the early estimates were that one to two per hundred thousand population had a neuroendocrine tumor. But as you can see from the figure at the bottom of this slide, there has been an increase in the incidence of neuroendocrine tumors. This is data from the Sierra Cancer
Registries, and in contrast to some of the other cancers, which have had a plateau or even a decrease in incidence, neuroendocrine tumor incidence is increasing. We think some of this is in part related to the classification changes that were made where more diagnoses were captured. But it also likely is in part related to the fact that patients are getting more frequent CAT scans that can find incidental diagnoses. Patients are also getting more frequent endoscopies, colonoscopies for screening that can find early gastrointestinal neuroendocrine tumors. We don’t yet understand what the role of lifestyle or diet or even medications like proton pump inhibitors are to this increased incidence that we are seeing.

I think it’s important to remember several key features about a neuroendocrine tumor as we approach each individual patient. And I’ll walk you through these, but they include the pathologic features of disease: where the primary tumor originated, and also whether or not this is a functional neuroendocrine tumor. And when I mention the functional status of a tumor, it really relates to whether or not a patient is experiencing symptoms related to any hormone that may be secreted. You may if you do blood work or do urine work find that there are elevations in hormones, but some patients are not symptomatic. The functional tumors that we'll mention are the ones where patients are symptomatic from the hormone excess.

Starting first with the pathology, it’s important as you look at a patient, as you look at the pathology reports, recognize whether this is a well differentiated or poorly differentiated tumor, and also to recognize the grade of the tumor.
Differentiation refers to how similar under the microscope the neuroendocrine tumor looks compared to normal neuroendocrine cells. Grade refers to the proliferative index of the tumor. These features have been associated with prognosis, as I'll show, and they also influence our management decisions.

In general, the low to intermediate grade tumors are ones that under the microscope have 20 or less mitoses per 10 high-powered field and a proliferative index as measured by Ki-67 of 20 or less. The poorly differentiated tumors are much more proliferative and look more aggressive histologically, and they have a much more aggressive biology than the disease that we'll be talking about. We typically approach the management of these cases, like we would, for instance, small cell lung cancer with platinum-based chemotherapy.

These figures give an illustration of how grade correlates with prognosis. The red lines in these figures refer to the high-grade tumors, whether we’re measuring it by Ki-67, or whether we’re measuring it by my mitotic count. But you can see that the survival of high-grade disease is much worse compared with low and even intermediate grade disease -- the blue and green lines.

Moving on to the primary site, I think it’s important to recognize that there are distinctions biologically, genetically, and even in response to treatment based on where the tumor originated. Take “carcinoid tumors.” We all refer to this, but the pathologists are actually moving away from the terminology of carcinoid, because it can be a bit ambiguous. It can be a bit confusing. And now we will typically refer to them as neuroendocrine tumor, and specify the site of origin. It’s sometimes hard to get rid of the terminology that you’ve been using for so long,
but when you look at pathology reports, very rarely now will you see something classified as carcinoid.

We know that these carcinoid tumors behave distinctly from pancreatic neuroendocrine tumors, and I'll show you some of that. We also know that they respond differently to treatment.

So, these are figures and tables that illustrate that the survival varies depending on primary site, whether you look at it from single institution database. On the left side of the screen is outcomes of patients at Dana-Farber. On the right side of the screen are the outcomes of patients based on larger Sierra Registry data. As you can see, and we'll focus on the Dana-Farber data, patients with small bowel neuroendocrine tumors, the green line, have a survival that's better than pancreatic neuroendocrine tumors. And this is likely related to biologic and even genetic differences in the tumor. The same pattern is seen when you look at the registry data: differences in outcome, differences in survival based on where the tumor started.

So, because survival varies based on primary tumor site, and because we also see that response to treatment varies according to primary site, we now have distinct treatment approaches and even clinical trials for patients who may have pancreatic or non-pancreatic neuroendocrine tumors.

Finally, I just want to spend a few minutes talking about the functional status of tumors. As I mentioned, functional neuroendocrine tumors are tumors that secrete hormones that lead to symptoms of the hormone excess. In carcinoid tumors the disease secretes serotonin and other neuropeptides. About
10 to 20 percent, depending on what study you look at of patients who have small intestinal carcinoids or small intestinal neuroendocrine tumors, experience a carcinoid syndrome. And because of these hormones, patients will experience flushing, diarrhea. They may experience wheezing and shortness of breath related to bronchoconstriction. Some patients may experience palpitations, and with long-standing carcinoid syndrome and serotonin excess, there can be development of valvular heart disease primarily on the right side of the heart.

Pancreatic neuroendocrine tumors also can be functional versus non-functional. About 60 to 70 percent of pancreatic neuroendocrine tumors are non-functional. There are about 30 to 40 percent that are associated with symptoms of hormone hypersecretion. The table below lists some of the more common hormones that are secreted by pancreatic neuroendocrine tumors; for instance, gastrin, glucagon, insulin, and VIP. The symptoms that patients will experience vary depending on the hormone. Ulcers and diarrhea, if it’s a gastrinoma. A very classic skin rash called necrolytic migratory erythema for glucagonoma, hyperglycemia for glucagonoma, symptoms of low blood glucose for insulinomas, and very profuse secretory diarrhea for VIP illness associated with a lot of electrolyte abnormalities.

As you think about the workup of patients with neuroendocrine tumors, it will include both imaging as well as blood and urine tests. The imaging will consist of cross-sectional imaging with either a CAT scan or MRI. Octreotide scans are very helpful for localizing disease and also assessing for whether or not the disease expresses somatostatin receptors. For patients with carcinoid
syndrome, if you want to evaluate for valvular heart disease, echocardiogram can be critical.

Blood and urine tests that can be helpful include a blood test for chromogranin A, which is a peptide that can be secreted by neuroendocrine tumors. If patients have symptoms of carcinoid syndrome, particularly if it’s a small bowel neuroendocrine tumor, 24-hour urine 5-HIAA, which is, you know, a breakdown product of serotonin, can be helpful. And depending on symptoms that patients may have, you may want to check some of the other hormones that I had run through when we were talking about pancreatic neuroendocrine tumors.

It’s also important to recognize that although we think of these hormones and blood tests as being specific to neuroendocrine tumors, they’re not completely specific. For instance, with chromogranin A, one of the very common reasons why we might find an elevation is because the patient is on a proton pump inhibitor. Most everybody these days seems to be on a proton pump inhibitor, so it’s very helpful to ask them if they’re on it so that you know what to make of the blood test result. And 24-hour urine 5-HIAA can be affected by diet and how much serotonin is in a diet. So you also have to make sure that patients are adhering to the diet when they’re doing the collection.

With that information in mind, I’m going to turn it over to Robin to run through a case. I just wanted to mention that the basic management principles, as we approach patients with neuroendocrine tumors, is to resect surgically all limited and sometimes limited metastatic disease. It’s also important to recognize that when we’re treating patients with advanced disease, we have to worry about
controlling hormone excess for patients with functional tumors and then also controlling growth of disease.

**DR. ROBIN SOMMERS:** There’ll be two cases that will be woven through this presentation, and the first one we’ll talk about is a 58-year-old male who presents to the emergency room with complaints of abdominal pain. He had imaging studies done that revealed a mass at the head of the pancreas. He underwent a Whipple procedure. Pathology revealed a well to moderately differentiated 2-cm pancreatic endocrine tumor. No lymph or vascular invasion, and seven peripancreatic lymph nodes were negative.

And so he had the surgery, path. He’s followed closely; clinical evaluation, labs, and serial scans. Surveillance scans down the road showed multiple hepatic lesions showing mild enhancement concerning for metastatic disease. CT guided biopsy was positive for metastatic low-grade neoplasm. LFTs, insulin, C-peptide level, and chromagranin A were all negative. An octreoscan was completed on this patient and he had uptake in the liver. The patient is asymptomatic at this time and this just shows you this patient now had multiple liver lesions, and you can see just looking at it because they’re hypervascular, they’re very, very difficult to see on scans. The arrows point to where this lesion was found. We really wanted to kind of get a sense for that, and so an octreoscan was taken and this shows where it lit up. This was what we call octreotide avid disease.

Which of the following management options would you recommend on this patient with low volume hepatic disease and is asymptomatic? A somatostatin
analog? Observe the patient? Serial scans and follow with markers? Hepatic regional therapy? Surgery? Or initiate everolimus or sunitinib?

Exactly the choices that I was expecting to see here. The answer in this particular case was observe serial scans and markers, but certainly, somatostatin analogs would have been a reasonable choice, too. I’m going to turn this over now.

**DR. JENNIFER CHAN:** I will be revealing with you the options for disease control in pancreatic neuroendocrine tumor. As Robin mentions, somatostatin analogs are an option for our patients. Somatostatin analogs have been a mainstay of the treatment for patients with neuroendocrine tumors for decades. They bind to somatostatin receptors and are highly expressed in neuroendocrine tumors. Some of the more common somatostatin analogs that are in clinical use include both octreotide and lanreotide, which have high affinity to the receptor subtypes 2 and 5. We know that the somatostatin analogs, by binding to the receptors, can lead to a decrease in hormone secretion and improvement in symptoms related to hormone excess.

We also now have randomized data from two clinical trials showing that the somatostatin analogs can improve disease control and have an antiproliferative effect. The first study that was conducted was the PROMID Study. And this is in small bowel or mid-gut neuroendocrine tumors. Patients with metastatic disease were randomized to receive either octreotide or placebo. The results of this study show that the time to tumor progression was longer in patients who were receiving octreotide compared with placebo. It was 14.3
months in the octreotide receiving patients compared to six months in the placebo arm.

The CLARINET study was a more recent study that was done looking at the efficacy of lanreotide and in this study patients with a broader range of neuroendocrine tumors including pancreas, as well as other GI neuroendocrine tumors, were randomized to receive lanreotide or placebo. The results of the study demonstrated that there was improved progression free survival in patients receiving lanreotide. The median survival was not reached in patients receiving lanreotide compared to a median progression free survival of 18 months in the placebo-containing group.

It’s interesting to look at the differences in the numbers. It’s very hard to do cross trial comparisons, though. It’s probably not statistically valid to do cross trial comparisons, because these populations are very different. In the CLARINET Study, there were patients who had stable disease at the time of study entry. So when we look at the data of neuroendocrine tumors, it’s important to recognize what patient population you’re examining. Was it low grade? Was it intermediate grade? Were the patients progressing at the time of the study entry or not? I’ll show you some other studies, but keep those features in mind.

It’s also important to recognize that there are side effects of somatostatin analogs. They include disordered glucose regulation by the octreotide or lanreotide’s effect on the hormones insulin, glucagon, as well as growth hormone. You can see both hypoglycemia, as well as hyperglycemia. Thyroid disorders can develop to octreotide, and lanreotide can decrease thyroid
stimulating hormone release. Cardiovascular disorders can be seen, including bradycardia and sometimes other rare conduction abnormalities. B\(_{12}\) deficiency is observed in patients receiving somatostatin analog, so periodically, it is worth checking vitamin B\(_{12}\) levels, as well as thyroid hormone levels.

And it’s also important to recognize that these somatostatin analogs can affect gall bladder motility and patients can develop gallstones or gall sludge, which can lead to cholecystitis and pancreatitis. It’s important to follow these symptoms closely. Consider getting an ultrasound if you’re worried about symptoms. And some patients may actually need a cholecystectomy in order to manage these symptoms.

Other agents that are active in pancreatic neuroendocrine tumor include the mTOR inhibitors. Activation of the mTOR pathway, via insulin growth factor 1, is implicated in the proliferation of neuroendocrine tumors. We’ve also seen that in sporadic pancreatic neuroendocrine tumors, there’s down regulation of the tumor suppressors P10 and TSC2 that lead to activation of this pathway. This pathway can be inhibited by mTOR inhibitors like everolimus.

Another pathway that’s active in neuroendocrine tumors is the VEGF pathway. Neuroendocrine tumors are very vascular and VEGF and VEGF receptor over expression has been seen in both carcinoid and pancreatic neuroendocrine tumors. We can block this pathway with monoclonal antibodies, such as bevacizumab, as well as the tyrosine kinase receptors that include sunitinib, sorafenib, and pazopanib.
Both sunitinib and everolimus have been studied in large randomized studies compared to placebo. Both have been shown to slow disease progression and are associated with improved progression free survival. They’ve never been compared head-to-head, so we don’t know the appropriate sequence of therapy. Both are appropriate options. Again, it’s not statistically valid to do cross-trial comparisons, but I’m going to do so anyway. When you look at the results of patients who receive both sunitinib and everolimus in these studies, the results look pretty similar. You know, even when you look at the progression free survival results compared to placebo, they’re not strikingly different. The other thing to notice is that the objective response rates to both agents are low in the single digit percent range.

Where they do seem to differ, though, as many of you know, is in their side effect profile. Sunitinib, like other tyrosine kinase inhibitors, is associated with hypertension, hand-foot syndrome, fatigue. Everolimus and the mTOR inhibitors are associated with pneumonitis, hyperglycemia, sometimes skin rash. So, while it may not be efficacy or knowledge about efficacy differences that drive decisions, sometimes it’s patient comorbidities and worries about side effects that can influence which agent we choose.

Cytotoxic chemotherapy also is active in pancreatic neuroendocrine tumors, and it’s the alkylating agent. Streptozotocin was actually the first FDA approved agent for patients with advanced pancreatic neuroendocrine tumors. That approval was based in large part on some of the older studies, like the one shown on the right of the screen that demonstrated streptozotocin in combination
with doxorubicin was associated with survival benefit compared to another regimen of streptozotocin in 5-FU. The response rates that were seen in the study were striking. Over 70 percent of patients had response. But, it’s important to recognize that the response in that study was based on older criteria for response that were not the CAT scans that we use now, but even physical examination and blood work tests. In more recent studies, we’ve seen response rates that are not as high, but still 30 to 40 percent.

Another alkylating agent that is active and that are tolerated in streptasozin is gaining more traction and use in pancreatic neuroendocrine tumors, and that’s temozolomide. We’ve seen in both retrospective series, as well as prospective trials, are response rates that range from anywhere between 30 and 70 percent. I’d like to also highlight one regimen in particular and that’s the regimen of temozolomide and capecitabine. In a retrospective series from patients at Moffitt that was published by John Strosberg, the response rate was 70 percent. Quite impressive and, you know, response in our patients can translate into improved symptoms from bulk of disease. Response can translate into improved hormone symptoms, as well, by reducing hormone secretion.

So, because we saw such good response rates in that series with that combination, ECOG is now leading a randomized study in patients with pancreatic neuroendocrine tumors, that are advanced of looking at the combination of temozolomide and capecitabine compared with single agent temozolomide, to help us understand whether we should be using combination therapy versus single agent therapy in our patients.
Another study recently that looked at combination therapy was looking at combinations of the targeted agents, looking at a combination of the mTOR inhibitor everolimus with bevacizumab. Again, trying to inhibit at both the mTOR pathway, as well as the VEGF pathway, and this was CLGB807L1. We learned the results of this at ASCO this year. What you can see here is that the study was a positive study, in a sense that it met its primary statistical endpoint of trying to demonstrate improved progression free survival of the combination of everolimus and bevacizumab compared with everolimus alone. The other important thing to recognize is that the response rates to combination therapy were higher than what you would see with single agent therapy with everolimus alone.

We also saw that the adverse events in the combination arm were higher. 81 percent of patients receiving everolimus and bevacizumab as a combination had grade 3/4 adverse events compared with only 49 percent in the everolimus arm. Many of these toxicities could be medically managed. Hypertension could be managed. Hyperglycemia could be managed. There does raise the question of, you know, are combinations the right choice for patients when we’re also worried about quality of life in these patients? And it may be that although we know that combinations are more active, we need to actually know how to use these combinations for how long and in which patients.

The other things, beside cytotoxic chemotherapy, that can achieve response in neuroendocrine tumors are liver directed therapies. So, for patients with liver predominant disease, it’s important to recognize that we aren’t just
limited by medical therapies, but we can consider surgery for patients who have
limited metastatic disease in the liver. Also, hepatic artery embolization is
something to consider with patients who might have more disease than can be
resected. But, again, these are both effective modalities for trying to control
disease and also hormone symptoms related to disease. I'll turn it back over to
Robin to finish off the case.

DR. ROBIN SOMMERS: To get back to the case. The patient that we had
spoken about, that we were observing and following with clinical evaluation labs,
undergoes restaging scans and shows mild progression of disease within the
liver, and now he’s symptomatic with some fatigue. Which one of the following
options would you recommend at this time? Initiating a somatostatin analog?
Adding sunitinib or everolimus? Chemotherapy? Or referring the patient for a
hepatic artery embolization?

Excellent choices again. The answer was initiating a somatostatin analog.
The patient was started on the somatostatin analog and given monthly, and then
was followed by serial exams and interval imaging and markers. Three years of
being on a somatostatin analog, the patient shows mild interval increase in liver
lesions. What management options now, with this patient that’s been on
somatostatin analog for three years, what would you offer? Chemotherapy?
Initiation of sunitinib or everolimus? Hepatic directed therapy? Or referring the
patient for peptide receptor radionuclide therapy, which is PRRT, which you’ll be
hearing about?
So, we have about half the audience saying sunitinib or everolimus, the other third of the audience saying PRRT. And the correct answer in this instance was initiating the patient on sunitinib or everolimus. And as Dr. Chan had mentioned earlier, we really don’t have any sequencing on which one. Again, it’s really dependent on the patients’ overall status and their underlying comorbid conditions.

The MD reviews the potential treatment options and makes the decision with the patient. The patient is going to start on everolimus. The patient receives all the educational material. The consent form is signed. One of the biggest things that we are experiencing right now with our patients that are on oral chemotherapy - do any of you have policies in place right now at your institutions or practices for patients that are on oral chemotherapies? I see a few hands out there. It was one of the bigger things that, you know, I actually saw in our practice, and we’ve all seen about five years ago when I went back for my doctorate degree. Part of my capstone project was on oral medication adherence. It was something that I saw in the practice that we were losing the checks and balances. Those patients that were going over to the infusion room - we had our nurses and, you know, there was like a quadruple check system. We lost that with oral chemotherapy when we were giving the patient the prescription or, at least, sending the prescription by fax to the pharmacy. We didn’t really have those safety checks in place. We talk about refills, and do we give refills with these oral meds or not? Do we want a patient that may not be compliant or
adherent and come back to our clinic, have five refills, and keep going back to the pharmacy?

So, you know, we really thought long and hard about what kind of policy we were going to be put in place. The pharmacy systems are another thing. Our patients are put on sunitinib or everolimus. You want the patient to start the prescription, and you don’t want to start three weeks from now. We made a decision in our practice that all the prescriptions would be faxed to our oncology pharmacy. It doesn’t mean that the patient will be able to get it there, but they wouldn’t leave the building until we knew exactly who was going to be filing it.

Most payers nowadays are requiring that these drugs go through specialty pharmacies. I think, again, it’s pricing issues and there are safety issues involved. Our retail pharmacists may not really have given out these prescriptions much before. They may not have a list of all the medications that the patient’s on. So, there’s lots of these little different little things in the system. One thing could go wrong, and we could have some issues in terms of side effects, etc.

With that in mind, we have a policy right now, in a way, was based on two pilot studies that we did at Dana-Farber. One was my capstone project and another one was in the thoracic group caring for patients that were getting Tarceva. And we found, based on best evidence available - it wasn’t a randomized trial, and this was from doing a literature review-- that really touching base with the patient closer by phone and really reviewing their educational material with them, and then having a nurse follow up with a phone call within 72 hours. Because you’re going to catch any of those discrepancies that the patient
may have, whether it’s on knowledge based on management of side effects or it’s on administration questions, et cetera. So, we actually have a policy in place. It went much bigger. The VP of Safety got involved. There were physicians on the council. There were pharmacists that were involved. Nurses were involved. Advanced practice nurses were involved. That all sat down, and we actually used the ASCO and the ONS guidelines, also, for oral chemotherapy administration.

The pharmacy will contact our patients within 24 hours, and so we have a treatment plan. We’re on EPIC, and the prescriptions get faxed down to our pharmacy. That triggers the pharmacist into a little queue that the patient’s been put on oral chemotherapy, and they call the patient within 24 hours. Within that, there’s also a little box that everyone gets notified, so the pharmacist then notifies our program nurses. They make a phone call to the patient within 72 hours, again, to kind of do that double-check system on their knowledge base.

The first time that the patient’s put on an oral medication, we usually have them come back if distance is not a big issue. We like to see them back in two weeks because you really want to kind of have that quick toxicity check initially, so that you can catch anything earlier and they’re not waiting a whole month. I think we’ve all seen those patients that have tried to tough it out with mucositis, diarrhea, etc.

This patient in particular came back for a follow-up visit with us, and on initial evaluation, certainly had evidence of grade 2 mucositis, but he decided to stop the med on his own. Two days prior to his presentation, which I’m glad he did, but again, encouraging our patients to call with any questions or concerns,
needed to be reiterated. So the therapy was held. The patient came back again after the mucositis symptoms had resolved. This was really two weeks later. Now he initiated therapy with a dose reduction of 5 mg. Right now he’s doing quite well on treatment, but he wonders what his other treatment options are that exist for the future.

The NCCN guidelines that we all refer to often actually have listed in it now, which we had heard from Dr. Chan certainly about, is octreotide or lanreotide as being options, if they were already on them, certainly considering everolimus, sunitinib, cytotoxic chemotherapy, hepatic regional therapy, etc. This helps also, because for all of you that have written prescriptions were done, and we get a little kickback from the insurance companies for the cost of these drugs, etc. We typically have found now that the payers are referring to the NCCN guidelines, and certainly for some of our drugs that we prescribe that are “off-label”, you know, we have phase 2 studies, etc. cetera, that will submit the abstract with the prescription to the payers. I’ll turn it over to Dr. Chan now.

So, this is case number two and we’re just going to switch gears a little bit. I’ll mention carcinoid here because it’s going to be the other half of the presentation that we’re going to talk about. This is a patient with a functional tumor; 54-year-old man who presents with anxiety and hypertension, has some flushing, loose stools, and some pain after eating. And, you know, typical of what was reminiscent of our patients that have these intestinal tumors, was diagnosed with irritable bowel syndrome and had that diagnosis for a while. After
experiencing months of symptoms, he goes to a gastroenterologist and undergoes further testing.

CT scan shows a mass. With these small bowel carcinoid tumors, it’s not uncommon to see a mass in the mesenteric area, and it’s usually fibrosis that can cause symptoms. He’s got disease that’s hyperenhancing lesions throughout his liver that are concerning for metastatic disease. He has a biopsy; it’s positive for metastatic low grade tumor. He has an arterial scan, it shows uptake in the liver. Chromogranin A level and a 24-hour urine for 5-HiAA are elevated and baseline echocardiogram is normal. So, now I'll turn over the management of the syndrome to Dr. Chan.

**DR. JENNIFER CHAN:** Thanks. As I mentioned, the somatostatin analogs have for years been the mainstay of treatment for our carcinoid tumors, carcinoid syndrome, and other functional tumors by reducing hormone levels and symptoms related to hormone excess. This is a figure that was done from one of the early studies on octreotide showing that the vast majority of patients had improvement in both flushing and diarrhea. We also saw a drop in the 24-hour urine 5-HiAA. So, octreotide has been approved and is FDA indicated for treatment of carcinoid syndrome. Lanreotide is, as I showed you before, indicated for growth and tumor control. Other studies in the past, though, have looked at the effects of lanreotide on both symptomatic response and biochemical response, and have seen similar results compared with octreotide.

One novel way to try to treat carcinoid syndrome is by targeting serotonin synthesis. Although most patients on somatostatin analogs will have symptom
improvement, some patients actually over the long run may need additional control. Telotristat etiprate is a novel oral inhibitor of tryptophan hydroxylase, which is the rate-limiting step in serotonin synthesis. Early studies that were done with this agent show that it was well tolerated, and also was helpful for reducing symptoms of carcinoid syndrome and also dropping 24-hour urine 5-HiAA levels.

Based on those earlier studies, the TELESTAR Study was performed. This was a randomized placebo controlled trial of patients with refractory carcinoid syndrome that was defined as four to 12 bowel movements per day on a standard dose of octreotide. Patients were randomized to receive during a 12-week period either placebo or two different dose levels of telotristat; 250 mg three times a day or 500 mg three times per day. The primary endpoint of the study was to look at the reduction in bowel movement frequency. As you can see from both the green and the blue line, patients who were receiving telotristat had a significant reduction in bowel movement frequency. The results of this study were just announced a few months ago, so you may be hearing more about this agent.

Also, what was part of the study was to look at 24-hour urine 5-HiAA levels. Those also did drop, as you would expect in patients receiving telotristat. The reduction was higher in the patients receiving the higher dose.

I want to end by discussing options for disease control. The second element to think about in patients with functional tumors, not just the hormone excess, but controlling growth. And these are the NCCN guidelines for how to manage neuroendocrine tumors of the GI tract, lung, and thymus. I'll highlight
that. As of now, the NCCN guidelines include octreotide or lanreotide for tumor control. But, as you look at the other options, notice that they’re category 2B and 3, so until now, has been more limited data about how effective other agents other than somatostatin analogs are. But, again, just in the last couple of months, we’ve seen results from two very large positive placebo controlled studies that I’ll review briefly with you that I think in the future are really going to change the options that we have to offer our patients.

You’ve seen this slide before and, again, it’s to reiterate that the somatostatin analogs, both octreotide and lanreotide, can slow tumor growth. The mTOR inhibitor everolimus has also been evaluated as a strategy for controlling growth in patients with neuroendocrine tumors that don’t originate in the pancreas. And in the RADIANT-2 Trial, patients with progressive metastatic low to intermediate grade neuroendocrine tumors associated with carcinoid syndrome. Again, these functional tumors were randomized to receive in addition to octreotide, everolimus or placebo.

Although the study did demonstrate that patients receiving everolimus had improved progression free survival compared with placebo based on local radiology review, the study did not meet its primary endpoint of demonstrating a statistically significant improvement in progression free survival based on central radiology review.

Everolimus was studied more recently in a follow-up study, which was the RADIANT-4 Study, again, just announced a couple of months ago at the European Society of Medical Oncology Conference. In this study, non-functional
tumors originating in the lung or GI tract that were progressive, those patients were randomized to receive either everolimus or placebo, again, looking at progression free survival as the primary endpoint.

What you can see from these Kaplan-Meier figures, the patients receiving everolimus had a significantly longer progression free survival compared with those receiving placebo; 11 months compared with 3.9 months. So, this will in the future, we hope, be another option to offer our options with carcinoid tumors.

Peptide receptor radionuclide therapy is another treatment modality specific to neuroendocrine tumors, and this consists of a somatostatin analog that is chelated with a radionuclide. The radionuclides that are more commonly used now include yttrium-90 or lutetium-177, and these agents can deliver tumoricidal doses of radiation to somatostatin receptor positive tumors.

The results of the NETTER-1 Study were announced a couple of months ago at that same conference and this was a phase III study of lutetium DOTATATE versus high dose octreotide. In this study, patients with progressive somatostatin receptor positive mid-gut, so small intestinal neuroendocrine tumors, who were experiencing progression of disease on standard dose octreotide were randomized to receive either Lutetium 177 DOTATATE or a high dose of octreotide LAR above label doses of 60 milligrams every month.

What you can see from this Kaplan-Meier figure is that the patients receiving lutetium 177 DOTATATE had a significantly longer progression free survival compared with patients receiving high dose octreotide. The median progression free survival in the lutetium patients had not been reached at the
time the study was analyzed compared to 8.4 months in patients receiving placebo.

We’re awaiting longer-term follow-up about adverse events, but so far what was reported, the study looks pretty good. In the United States this is not yet widely available, so patients have gone overseas, for instance, to Europe. There are other centers in North America, like Canada, that are offering this. But, hopefully, in the future as more programs adopt this therapeutic modality and as it goes through regulatory issues and if it gains approval, this may be another option to offer patients in the future.

Getting back to our patient, the middle-aged man who was having postprandial flushing, the diarrhea, and had what looks to be a metastatic mid-gut neuroendocrine tumor, what would we recommend? A. Observation; B. somatostatin analog therapy; C. hepatic artery embolization; D. hepatic resection; or E. everolimus or sunitinib? The overwhelming majority vote for somatostatin analog, which is what Robin and I also chose.

So, in conclusion, I think as you’ve heard from both Robin and me, multidisciplinary approach is critical to management of this disease. There are so many different options that we have to offer our patients, ranging from surgery, interventional radiology, and medical therapy. So, it’s important to integrate all disciplines.

Somatostatin analogs are a mainstay in the treatment of both functional endocrine tumors to help with the symptoms of hormone excess, and they also can slow disease progression. For patients with carcinoid syndrome, novel
agents like telotristat also hold a lot of promise for helping patients with symptom control.

Multiple options exist for disease control, and we reviewed that data looking at hepatic directed therapies with embolization or surgery for hepatic predominant disease, alkylating agents to help site or reduce pancreatic neuroendocrine tumors. Sunitinib and everolimus are approved in pancreatic neuroendocrine tumors. We have now seen everolimus improve progression free survival in non-functional lung and GI neuroendocrine tumors. A newer technology, PRRT, also improves progression free survival in mid-gut neuroendocrine tumors. And, finally, in a disease where at least until now there have been limited options and as we try to advance the care of our patients, I think it’s also important to recognize that clinical trial enrollment is encouraged, as well. And as Robin mentioned, collaborative practice models very much can enhance patient care.

We want to thank you for listening to us today and we’ll welcome any questions. There’s one. I saw one hand in the front.

ATTENDEE: Are you recommending that people coat the everolimus anymore with something to help prevent mucositis?

DR. ROBIN SOMMERS: No, we’re not. We haven’t recommended it where I work, but I have heard of other institutions that have coated it for that very reason.

DR. JENNIFER CHAN: There’s a question up front.
ATTENDEE: When do you do any liver directed therapies? Is it just when they are symptomatic? Is there any survival advantage to jumping on top of it sooner if there’s growth and progression?

DR. JENNIFER CHAN: That’s actually never been well established in terms of what is the optimal time for liver directed therapy. Typically, we will approach our patients with somatostatin analog therapy as a first-line therapy. They’re well tolerated. There’s a lot of data that has established efficacy. But, at the time of progression and maybe even before progression if patients have large volume disease and are asymptomatic, we’ll think about a liver embolization procedure.

ATTENDEE: As far as routine imaging do you find that to be advantageous or is it about the same if you wait until they’re symptomatic and then start treatment?

DR. JENNIFER CHAN: I think there are two approaches; one is to image based on symptoms, but the other is to image on some sort of schedule, whether it’s three to six months, because you may not detect disease growth. Some patients may actually be asymptomatic in the setting of progression of disease. As we now have agents that can slow disease progression, I think it’s important to recognize image for symptoms, but also image periodically so that you get a better sense of disease control. I think we typically will image on the every three to six month period, and whether to do it sooner or on the longer end, I think you’ll get a better sense as you watch patients how their disease is behaving. Some patients with very indolent disease, I think it’s fine to image on the every
six months, but there are some patients who even at the every three months, you’ll see some progression where you might want to offer therapy sooner. So, imaging at the three month point is also reasonable. Many of the clinical trials that I mentioned to you required imaging on the three month period.

ATTENDEE: I’ve got a question about the dosing of the somatostatin analogs on somebody with renal dialysis. Also, are you using more lanreotide now versus the other drug?

DR. JENNIFER CHAN: So, I think that the question about what to do in patients with dialysis, there are recommendations to start at a lower dose of the somatostatin analog. The lanreotide and octreotide have never really been compared head-to-head. I think lanreotide’s the newer somatostatin analog, and because it’s been at market now for a longer period of time, I think we’re seeing patients receiving it more just as people become more aware of it. But, we’ve not had any data to say that one is better than the other, and both are appropriate agents to consider depending on the situation.

DR. ROBIN SOMMERS: And patients are actually coming in and that’s one of the questions there. I’ll tell you the patients I find, anyway in our practice that have been on octreotide for five and eight and ten years, they’re very reluctant anyway to switch, but they just want to know a little bit more about the agent and the differences between the two.

ATTENDEE: You mentioned that PPIs can affect the CgA levels. For our patients who are on PPIs, is there maybe a time that we can have them go off of their medication and then get a more accurate CgA reading?
DR. JENNIFER CHAN: Yes, and that’s been looked at and the recommendations from the labs are to stop for two weeks. I think the one time you do have to be careful about stopping PPIs in patients where you think they may have, for instance, a gastrinoma, you really don’t want to have that rebound effect where the acid can become problematic. But, in many of my patients, for instance, small mal neuroendocrine tumors not worried about being off of a PPI, I’ll have them stop for two weeks and use other agents, like H2 blockers, in that period.

ATTENDEE: I had another question about SBRT. Is there any rule for SBRT as a hepatic directed therapy?

DR. JENNIFER CHAN: We typically thought of these neuroendocrine tumors, especially the low grade ones, as not being radiation sensitive. So, there’s not a lot of literature in the data about using SBRT to treat liver predominant disease. It’s mainly to think about either surgery or if they’re not surgical candidates but have a small solitary lesion, maybe ablate. Many of our patients will have what Robin had showed with the imaging is it’s kind of more diffuse disease, and that’s where the embolization strategies can be very effective.

DR. ROBIN SOMMERS: Thank you very much.

[END]