Pancreatic Neuroendocrine Tumors
Webinar

Presented by
Pancreatic Cancer Action Network
www.pancan.org

June 22, 2012

James C. Yao, MD
Associate Professor and Deputy Chair,
Gastrointestinal Medical Oncology
University of Texas MD Anderson Cancer Center
PANCREATIC NEUROENDOCRINE TUMORS

James C. Yao, MD
Associate Professor and Deputy Chair,
Gastrointestinal Medical Oncology

Disclosures

- Consultancy
  - Ipsen, Lexicon, Novartis, Pfizer
- Research support
  - Novartis Oncology
- I will discuss the following off label use and/or investigational use in my presentation:
  - Temozolomide, BEZ235
Exocrine
- Digestive enzymes
- Sodium bicarbonate

Endocrine
- Islets of Langerhans
- Hormones to regulate GI function
- Hormones to regulate metabolism

Endocrine cells in the islet of Langerhans

**Insulin**
- Glucagon
- Somatostatin
- Pancreatic polypeptide

http://seungkimlab.stanford.edu/islet.html
Pancreatic NET: Benign versus malignant

- Criteria for malignant potential
  - Size, invasion, spread or metastasis
- Insulinoma < 1 cm are generally considered benign
  - Diagnosed early because of intense symptoms
- Malignant pancreatic NET
  - Mostly non-functional
  - 1-4% of new pancreatic cancers diagnosed each year
  - 10% of all patients alive with pancreatic cancer


Malignant pancreatic NET is a different disease from pancreatic adenocarcinoma

Pancreatic cancer
SEER 18, 2000 – 2009, all stage

NET (n = 2,654)
Median survival 41.2 months
5-year survival 41%

Non-NET (n = 71,070)
Median survival 4.7 months
5-year survival 4%

Malignant pancreatic NET each year

Approximately 3 per million per year

Conservative estimate
Many small pNET are not reported to SEER

Adapted from: Yao JC et al, JCO 2008

Prevalence of malignant pancreatic NET

- Projected US prevalence using 2000 census data is 5,206 in 2006
- 31-year limited duration prevalence using SEER 9
- Among ~9% of US population – 471 cases
- Autopsy study
  - >11,000 cases from Hong Kong
  - .1%


Lam KY, Lo CY. Ear J Surg Oncol 1997;23:36-42
Pancreatic NET

- Most pancreatic NET are not linked to any genetic cancer syndrome
- Small fraction pancreatic NET arise in setting of inherited cancer syndrome
  - MEN1 – hyper parathyroid, pituitary adenoma, carcinoids of lung and thymus
  - TSC2 – Subependymal giant-cell astrocytoma, angiomyolipomas
  - NF1, vHL

pNET: Survival and stage

<table>
<thead>
<tr>
<th>Stage at diagnosis</th>
<th>Survival by stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localized</td>
<td>&gt; 10 years</td>
</tr>
<tr>
<td>Regional</td>
<td>111 months</td>
</tr>
<tr>
<td>Distant</td>
<td>27 months</td>
</tr>
<tr>
<td>Unknown</td>
<td></td>
</tr>
</tbody>
</table>

Functional pancreatic NET symptoms

- **Gastrinoma** (gastrin)
  - Reflux
  - Ulcer
  - Diarrhea
- **Glucagonoma** (glucagon)
  - Diabetes
  - Rash
  - Blood clot
  - Weight loss
- **Insulinoma** (insulin)
  - Low blood sugar
  - Weight gain
- **VIPoma** (vasoactive intestinal peptide)
  - Diarrhea

Non-functional pancreatic NET and symptoms at diagnosis

- Asymptomatic and incidentally found
- Symptoms in some patients based on location of primary tumor
  - Pancreatic head: Jaundice due to biliary obstruction
  - Pancreatic tail: Bleeding from stomach due to occlusion of splenic vein and gastric varices
Limited options for advanced pancreatic NETs prior to May 2011

- **Hormonal syndrome** → **Octreotide** → **Disease progression**
- **pNET** → **Oncologic control** → **Streptozocin-based Chemotherapy**

---

Pancreatic NET
Not everyone needs treatment
Pancreatic NET
Streptozocin-based chemotherapy

- Oral chemotherapy
  - Not FDA approved for pancreatic NET
- Reported response rates varies from 8% to 70%
- Analyses of prospective studies suggest response rate approximately 30%
- No prospective data to define if combination is better than single agent
- Risk of unusual infections with prolonged use

Temozolomide-based chemotherapy
mTOR

NASA photo – Island of Rapa Nui

[Diagram of mTOR pathway with various proteins and signaling pathways]

Nutrients
Glucose
Amino acids

Survival
Growth and proliferation
Metabolism
Apoptosis

mTOR inhibitor

mTOR

AKT

PTEN

TSC1/2

NF1

PI3K

Pyruvate

VHL

Protein synthesis
M. D. Anderson Phase II study of Everolimus (initiated in 2005)

Patient with gastrinoma and gastric carcinoid

Patient 1
57/female
MDACC
Depot octreotide, diazoxide, dexamethasone, and oral feeding q 2 hours and nocturnal continuous enteral feeding.
Normalization of glucose; discontinuation of diazoxide and nocturnal feedings
Partial response
16 months

Patient 2
40/female
MDACC
Depot octreotide, diazoxide, and glucose tablets.
Normalization of glucose; discontinuation of diazoxide and glucose tablets
Partial response
29 months

Patient 3
22/female
DFCI
Intermittent symptomatic hypoglycemia despite use of depot octreotide and diazoxide.
Normalization of glucose and discontinuation of diazoxide
Stable disease
6+ months

Patient 4
66/male
UCSF
Glucose control requiring nocturnal dextrose infusions
Normalization of glucose and discontinuation of nocturnal dextrose infusions
Stable disease
6+ months

Dramatic benefit in insulinoma

RADIANT-1: Patient in Stratum 2 (initiated in 2006)

-2 months baseline +4 months

Chemotherapy Everolimus + Octreotide

Patient remains on study 22+ months

RADIANT-3 Study Design
Phase III, Double-Blind, Placebo-Controlled Trial

Patients with advanced PNET, N = 410
PD within 12 mo
Stratified by: WHO PS prior chemotherapy

1:1 Randomize

Everolimus 10 mg/d + best supportive care* n = 207

Crossover

Placebo + best supportive care* n = 203

Multiphasic CT or MRI performed every 12 wk

Primary end point:
- PFS (RECIST)

Secondary end points:
- Response, OS, biomarkers, safety, and PK

*Concurrent somatostatin analogues allowed.

RADIANT-3
PFS by Investigator Review

Kaplan-Meier median PFS
Everolimus: 11.0 mo
Placebo: 4.6 mo
Hazard ratio = 0.35; 95% CI 0.27–0.45
P value: <.0001

No. of patients still at risk

<table>
<thead>
<tr>
<th></th>
<th>Everolimus</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>207</td>
<td>199</td>
<td>198</td>
</tr>
<tr>
<td>198</td>
<td>153</td>
<td>152</td>
</tr>
<tr>
<td>153</td>
<td>126</td>
<td>125</td>
</tr>
<tr>
<td>126</td>
<td>114</td>
<td>113</td>
</tr>
<tr>
<td>114</td>
<td>80</td>
<td>79</td>
</tr>
<tr>
<td>80</td>
<td>49</td>
<td>48</td>
</tr>
<tr>
<td>49</td>
<td>36</td>
<td>35</td>
</tr>
<tr>
<td>36</td>
<td>28</td>
<td>27</td>
</tr>
<tr>
<td>28</td>
<td>21</td>
<td>20</td>
</tr>
<tr>
<td>21</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>10</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

P value obtained from stratified 1-sided log-rank test
Hazard ratio is obtained from stratified unadjusted Cox model

# Everolimus: Treatment-Related Adverse Events

<table>
<thead>
<tr>
<th>Median treatment duration</th>
<th>Everolimus (n=204)</th>
<th>Placebo (n=203)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3 or 4</td>
</tr>
<tr>
<td></td>
<td>no. of patients (%)</td>
<td></td>
</tr>
<tr>
<td>Stomatitis*</td>
<td>131 (64)</td>
<td>14 (7)</td>
</tr>
<tr>
<td>Rash</td>
<td>99 (49)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>69 (34)</td>
<td>7 (3)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>64 (31)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Infections†</td>
<td>46 (23)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Nausea</td>
<td>41 (20)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>41 (20)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>40 (20)</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>39 (19)</td>
<td>0</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>35 (17)</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>35 (17)</td>
<td>12 (6)</td>
</tr>
<tr>
<td>Epistaxis§</td>
<td>35 (17)</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonitis§</td>
<td>35 (17)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>32 (16)</td>
<td>0</td>
</tr>
</tbody>
</table>

* Included in this category are stomatitis, aphthous stomatitis, mouth ulceration, and tongue ulceration
† All types of infection included
§ Included in this category are pneumonitis, interstitial lung disease, lung infiltration, and pulmonary fibrosis

---

## AE Management: Aphthous ulcerations

- **pNET**
  - Grade 1 or 2: 64% everolimus vs 17% placebo
  - Grade 3 or 4: 7% everolimus vs 0% placebo
- Advanced RCC patients: 44%
- Topical treatments are recommended, but alcohol- or peroxide-containing mouthwashes should be avoided
Angiogenesis

Sunitinib – Phase III Design

Eligibility criteria
- Well-differentiated, malignant pancreatic endocrine tumor
- Disease progression in past 12 months
- Not amenable to treatment with curative intent

Arm A
- Sunitinib 37.5 mg/day orally, continuous daily dosing (CDD)*
- Primary endpoint: PFS
- Secondary endpoints: OS, ORR, TTR, duration of response, safety, patient-reported outcomes

Arm B
- Placebo*

Randomization

N = 340 (planned)
N = 171 (actual)

Final analysis planned at 260 events
One interim analysis planned at 130 events

Sunitinib Phase III – Investigator PFS

- **Median PFS**
  - **Sunitinib**: 11.4 months (95% CI 7.4, 19.8)
  - **Placebo**: 5.5 months (95% CI 3.6, 7.4)
  - **HR = 0.418** (95% CI 0.263, 0.662)

- **Number at risk**
  - **Sunitinib**: 86
  - **Placebo**: 85

- **Time (months)**
  - **Sunitinib**: 30/86
  - **Placebo**: 51/85

- **Events**
  - **Sunitinib**: 30/86
  - **Placebo**: 51/85


Sunitinib: Treatment-Related Adverse Events

<table>
<thead>
<tr>
<th>Median treatment duration</th>
<th><strong>Sunitinib (n=83)</strong></th>
<th><strong>Placebo (n=82)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sunitinib: 4.6 mos</td>
<td>Placebo: 3.7 mos</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>All Grades</th>
<th>Grade 3 or 4</th>
<th>All Grades</th>
<th>Grade 3 or 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diarrhea</strong></td>
<td>49 (59)</td>
<td>4 (5)</td>
<td>32 (39)</td>
<td>2 (2)</td>
</tr>
<tr>
<td><strong>Nausea</strong></td>
<td>37 (45)</td>
<td>1 (1)</td>
<td>24 (29)</td>
<td>1 (1)</td>
</tr>
<tr>
<td><strong>Anemia</strong></td>
<td>28 (34)</td>
<td>4 (5)</td>
<td>22 (27)</td>
<td>3 (4)</td>
</tr>
<tr>
<td><strong>Vomiting</strong></td>
<td>28 (34)</td>
<td>0</td>
<td>25 (30)</td>
<td>2 (2)</td>
</tr>
<tr>
<td><strong>Fatigue</strong></td>
<td>27 (32)</td>
<td>4 (5)</td>
<td>22 (27)</td>
<td>7 (8)</td>
</tr>
<tr>
<td><strong>Hair color changes</strong></td>
<td>24 (29)</td>
<td>1 (1)</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Neutropenia</strong></td>
<td>24 (29)</td>
<td>10 (12)</td>
<td>3 (4)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Abdominal pain</strong></td>
<td>23 (28)</td>
<td>4 (5)</td>
<td>26 (32)</td>
<td>8 (10)</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>22 (26)</td>
<td>8 (10)</td>
<td>4 (5)</td>
<td>1 (1)</td>
</tr>
<tr>
<td><strong>Palmar-plantar erythrodysesthesia</strong></td>
<td>19 (23)</td>
<td>5 (6)</td>
<td>2 (2)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Anorexia</strong></td>
<td>18 (22)</td>
<td>2 (2)</td>
<td>17 (21)</td>
<td>1 (1)</td>
</tr>
<tr>
<td><strong>Stomatitis</strong></td>
<td>18 (22)</td>
<td>3 (4)</td>
<td>2 (2)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Dysgeusia</strong></td>
<td>17 (20)</td>
<td>0</td>
<td>4 (5)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Epistaxis</strong></td>
<td>17 (20)</td>
<td>1 (1)</td>
<td>4 (5)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Headache</strong></td>
<td>15 (18)</td>
<td>0</td>
<td>11 (13)</td>
<td>1 (1)</td>
</tr>
<tr>
<td><strong>Insomnia</strong></td>
<td>15 (18)</td>
<td>0</td>
<td>10 (12)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Rash</strong></td>
<td>15 (18)</td>
<td>0</td>
<td>4 (5)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Thrombocytopenia</strong></td>
<td>14 (17)</td>
<td>3 (4)</td>
<td>4 (5)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Mucosal inflammation</strong></td>
<td>13 (16)</td>
<td>1 (1)</td>
<td>6 (7)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Weight loss</strong></td>
<td>13 (16)</td>
<td>1 (1)</td>
<td>9 (11)</td>
<td>0</td>
</tr>
</tbody>
</table>

*Cardiac failure leading to death was reported in 2/83 (2%) patients on SUTENT and no patients on placebo.
Approved Therapy – Pancreatic NET
(after May 2011)

- Hormonal syndrome
  - Octreotide LAR
- pNET
  - Oncologic control
    - Everolimus
    - Sunitinib
    - High tumor burden
      - Chemotherapy
- Disease progression
  - Investigational agents
  - Regional therapy
    (No approved therapies are available)

Have we improved outcome?

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Median overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>**RADIAN 3 (phase 3)**¹</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Everolimus</td>
<td>207</td>
<td>&gt;36 months</td>
</tr>
<tr>
<td>Placebo</td>
<td>203</td>
<td>36.6 months</td>
</tr>
<tr>
<td><strong>Sunitinib phase 3</strong>²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sunitinib</td>
<td>86</td>
<td>30.5 months</td>
</tr>
<tr>
<td>Placebo</td>
<td>85</td>
<td>24.4 months</td>
</tr>
<tr>
<td><strong>Streptozocin-based chemo</strong>³</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Streptozocin fluorouracil</td>
<td>33</td>
<td>16.8 months*</td>
</tr>
<tr>
<td>Streptozocin doxorubicin</td>
<td>36</td>
<td>26.4 months**</td>
</tr>
</tbody>
</table>

¹Reported as 1.4 years. ²Reported as 2.2 years.
³Reported as 1.4 years. ⁴Reported as 2.2 years.

Initial therapy of pNET

- Bulky aggressive
- Low volume slow-growing
- Bulky slow-growing
- Low volume aggressive
- Medium disease burden
- Proliferative rate

Chemotherapy
Everolimus or Sunitinib
Surveillance SSA
Everolimus or Sunitinib

Multi-disciplinary approach

- Medical therapy
- Surgery
- Ablation
- Embolization
- Clinical trials

Coordinating team (Based on disease state)
Medical Oncology
Dietician
Surgery
Nursing
GI
Cardiology
Endocrine
Nuclear Medicine
Interventional Radiology
Radiology
Pathology

What is next at M. D. Anderson?

- Combination to further improve outcome
  - Everolimus + bevacizumab (completed)
  - Everolimus + IGF1 inhibitor (completed)
  - Everolimus + Pasireotide (to start soon)
  - Everolimus + radioembolization

- More complete blockade of PI3K/mTOR pathway
  - BEZ 235 inhibits TORC1, TORC2, and PI3K

PANCREATIC NEUROENDOCRINE TUMORS

James C. Yao, MD
Associate Professor and Deputy Chair,
Gastrointestinal Medical Oncology
Thank you for your participation

Pancreatic Cancer Action Network
www.pancan.org

If you have any questions about our Patient and Liaison Services (PALS) program, please contact (877) 272-6226 or e-mail pals@pancan.org.