Progress in the land of small tumors: Recent advances and future directions in advanced neuroendocrine tumors

James C. Yao, MD
Professor and Chairman, Gastrointestinal Medical Oncology
University of Texas MD Anderson Cancer Center
Continued rise in incidence of neuroendocrine tumors

Dasari et al, JAMA Oncology, In Press 2017
# Is NET still rare?

<table>
<thead>
<tr>
<th>Year</th>
<th>Annual incidence rate per 100,000</th>
<th>US prevalence count estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td>5.25</td>
<td>103,312&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>2012</td>
<td>6.98</td>
<td></td>
</tr>
<tr>
<td>2014</td>
<td></td>
<td>171,321&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>1</sup> 29-year limited duration prevalence. <sup>2</sup> 20-year limited duration prevalence

Shen et al, NANETS 2016
Dasari et al, JAMA Oncology, In Press 2017
Core pathways in pancreatic NETs

DNA damage repair
- MUTYH *
  - 6% 47%
  - 5% biallelic inactivation
  - 6% germline pathogenic
- CHEK2 *
  - 4% 49%
  - 2% biallelic inactivation
- BRCA2 *
  - 1% 9%
  - 1% biallelic inactivation

Chromatin modification
- SETD2
  - 5% 51%
  - 4% biallelic inactivation
- MLL3
  - 5% 10%

Altered telomere length
- DAXX
  - 22% 53%
  - 20% biallelic inactivation
- ATRX
  - 10% 19%

MTOR signalling
- PTEN
  - 7% 40%
  - 7% biallelic inactivation
- DEPDC5
  - 2% 49%
  - 2% biallelic inactivation
- PIK3CA
- AKT
- MTOR
- Cell growth
  - Cell proliferation
- Angiogenesis
- Autophagy

PSPN
- 0% 13%
EWSR1 fusion
- 3%

TSC1
- 2% 17%
TSC2
- 2% 43%
- 2% biallelic inactivation

Scarpa et al, Nature 2017
Chromosomal instability in pancreatic NETs

Yao et al, J Clin Oncol 34, 2016 (suppl; abstr e23284)
Genomic progression of pancreatic NET

1. MEN1
2. DAXX (ALT)
3. Chromosomal instability
4. MEN1
5. Chromosomal instability
6. DAXX (ALT)
Chromosomal instability in pancreatic NETs
Approved agents for oncologic control before 2011

- **pNETs**: Streptozocin
- **GI NETs**: None

**Treatments**

- **1900**
- **1980**
- **1988/89**
  - OCT SC
  - CS 14, 20
- **1992**
  - STZ combination: STZ pNET
- **1998**
  - LAN
  - Symptom control 14
  - OCT LAR
  - Carcinoid tumors 13, 26, 29
- **2000**
- **2005**
- **2009**
  - PROMID
  - OCT LAR: Antitumor activity 18, 21
- **2010/11**
  - Sunitinib phase III pNET 11, 12, 21, 23
- **2010**
  - RADIANT-3
  - EVE in pNET 11, 12, 32, 33
  - Sunitinib phase II pNET 11, 12, 21, 23
- **2015**
  - NETTER-1
  - 177Lu-Dotatate midgut NET

AC, atypical carcinoid; AJCC, American Joint Committee on Cancer; CS, carcinoma syndrome; ENETS, European Neuroendocrine Tumor Society; ESMO, European Society for Medical Oncology; EVE, everolimus; GEP, gastroenteropancreatic; GI NETs, gastrointestinal neuroendocrine tumors; LAN, lanreotide; LAR, long-acting repeatable; m, metastatic; NANETS, North American Neuroendocrine Tumor Society; NEC, neuroendocrine carcinomas; NET, neuroendocrine tumors; NF, nonfunctional; OCT, octreotide; pNET, pancreatic NET; SC, subcutaneous; STZ, streptozocin; TC, typical carcinoid; UICC, Union for International Cancer Control; WHO, World Health Organization

**US approval**

- **1982** STZ, pNET
- **1988/89** OCT SC CS
- **1992** STZ combination: STZ pNET
- **1998** LAN Symptom control
- **2000**
- **2005**
- **2009**
- **2010**
- **2015**

**US/EU approval**

- **1992** OCT SC CS
- **1998** OCT LAR, Carcinoid Tumors
- **2000**
- **2009** PROMID OCT LAR Antitumor activity
- **2010**
- **2015**

**EU approval**

- **2000**
- **2005**
- **2009**
- **2010**
- **2015**
AC, atypical carcinoid; AJCC; American Joint Committee on Cancer; CS, carcinoid syndrome; ENETS, European Neuroendocrine Tumor Society; ESMO; European Society for Medical Oncology; EVE, everolimus; GEP, gastroenteropancreatic; GI NETs, gastrointestinal neuroendocrine tumors; LAN, lanreotide; LAR, long-acting repeatable; m, metastatic; NANETS, North American Neuroendocrine Tumor Society; NEC, neuroendocrine carcinomas; NET, neuroendocrine tumors; NF, nonfunctional; OCT, octreotide; pNET, pancreatic NET; SC, subcutaneous; STZ, streptozocin; TC, typical carcinoid; UICC, Union for International Cancer Control; WHO, World Health Organization

Approved agents for oncologic control
- pNETs: Everolimus, sunitinib, lanreotide
- GI NETs: Lanreotide, everolimus
- Lung Nets: Everolimus

Other active agents
- pNETs: Temozolomide
- GI NETs: Octreotide, (177)Lu-DOTATATE

Approved agents for oncologic control before 2011
- pNETs: Streptozocin
- GI NETs: None
# Treatment Landscape for Advanced NETs

<table>
<thead>
<tr>
<th>Site</th>
<th>Octreotide</th>
<th>Lanreotide</th>
<th>(^{177}\text{Lu-DOTATATE})</th>
<th>Streptozocin</th>
<th>Sunitinib</th>
<th>Everolimus</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Disease status</strong></td>
<td>Tx naïve</td>
<td>Stable</td>
<td>Progressive over 3 yrs</td>
<td>Historical</td>
<td>Progressive over 12 mo</td>
<td>Progressive over 6 mo*</td>
</tr>
<tr>
<td>Lung</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RADIANT 4</td>
</tr>
<tr>
<td>Stomach</td>
<td></td>
<td>CLARINET</td>
<td></td>
<td></td>
<td></td>
<td>RADIANT 4</td>
</tr>
<tr>
<td>Pancreas</td>
<td></td>
<td>CLARINET</td>
<td>Historical</td>
<td>Phase III</td>
<td></td>
<td>RADIANT 3*</td>
</tr>
<tr>
<td>Small bowel</td>
<td>PROMID</td>
<td>CLARINET</td>
<td>NETTER-1</td>
<td></td>
<td></td>
<td>RADIANT 4</td>
</tr>
<tr>
<td>Appendix</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RADIANT 4</td>
</tr>
<tr>
<td>Colon</td>
<td></td>
<td>CLARINET</td>
<td></td>
<td></td>
<td></td>
<td>RADIANT 4</td>
</tr>
<tr>
<td>Rectum</td>
<td></td>
<td>CLARINET</td>
<td></td>
<td></td>
<td></td>
<td>RADIANT 4</td>
</tr>
</tbody>
</table>

*RADIANT-3 requires documentation of progressive disease (PD) in the prior 12 months. RADIANT-4 requires documentation of PD during prior 6 months.

PROMID: Octreotide LAR vs Placebo

Time to progression

- **Octreotide LAR**: 42 patients/26 events
  - Median 14.3 months [95% CI: 11.0-28.8]
- **Placebo**: 43 patients/40 events
  - Median 6.0 months [95% CI: 3.7-9.4]

### Endpoint Results

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Octreotide LAR</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious adverse events (SAEs), n (%)</td>
<td>11 (26)</td>
<td>10 (23)</td>
</tr>
<tr>
<td>Most frequent SAEs, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal (GI) tract</td>
<td>6 (14)</td>
<td>8 (19)</td>
</tr>
<tr>
<td>Hematopoietic system</td>
<td>5 (12)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>General health status (fatigue, fever)</td>
<td>8 (19)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>AEs causing discontinuation, n (%)</td>
<td>5 (12)</td>
<td>0</td>
</tr>
<tr>
<td>Bile stones, n (%)</td>
<td>5 (12)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Treatment-related deaths</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

CLARINET: Lanreotide Autogel vs Placebo

<table>
<thead>
<tr>
<th></th>
<th>Lanreotide n = 101</th>
<th>Placebo n = 103</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any treatment-emergent AE, n (%)</td>
<td>89 (88)</td>
<td>93 (90)</td>
</tr>
<tr>
<td>Related to treatment</td>
<td>50 (50)</td>
<td>29 (28)</td>
</tr>
<tr>
<td>Severe</td>
<td>26 (26)</td>
<td>32 (31)</td>
</tr>
<tr>
<td>Moderate</td>
<td>44 (44)</td>
<td>44 (43)</td>
</tr>
<tr>
<td>Mild</td>
<td>17 (17)</td>
<td>17 (17)</td>
</tr>
<tr>
<td>Any SAE,a n (%)</td>
<td>25 (25)</td>
<td>32 (31)</td>
</tr>
<tr>
<td>Related to treatment</td>
<td>3 (3)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Withdrawals due to treatment-emergent AE</td>
<td>3 (3)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Related to treatment</td>
<td>1 (1)</td>
<td>0</td>
</tr>
</tbody>
</table>

Treatment-related AE in ≥10% of patients, n (%)

<table>
<thead>
<tr>
<th></th>
<th>Lanreotide</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>26 (26)</td>
<td>9 (9)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>14 (14)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Cholelithiasis</td>
<td>10 (10)</td>
<td>3 (3)</td>
</tr>
</tbody>
</table>

Progression-free survival (PFS)

Lanreotide Autogel 120 mg vs placebo
- 32 events, 101 patients
- Median not reached

Placebo
- 60 events, 103 patients
- Median, 18.0 mo (95% CI, 12.1–24.0)

Lanreotide Autogel 120 mg vs placebo P = .001
HR = 0.47 (95% CI: 0.30, 0.73)

Sunitinib in pancreatic NET
PFS by Investigator Review

Median PFS
Sunitinib 11.4 months (95% CI 7.4, 19.8)
Placebo 5.5 months (95% CI 3.6, 7.4)
HR = 0.42  (95% CI 0.26, 0.66)
$P = .001$

### Sunitinib in pancreatic NET

#### Adverse events

<table>
<thead>
<tr>
<th>Event</th>
<th>Sunitinib (n = 83)</th>
<th>Placebo (n = 82)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All grades</td>
<td>Grade 1 or 2</td>
</tr>
<tr>
<td></td>
<td>Number of patients (%)</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>49 (59)</td>
<td>45 (54)</td>
</tr>
<tr>
<td>Nausea</td>
<td>37 (45)</td>
<td>36 (43)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>28 (34)</td>
<td>24 (29)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>28 (34)</td>
<td>28 (34)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>27 (32)</td>
<td>23 (28)</td>
</tr>
<tr>
<td>Hair-color changes</td>
<td>24 (29)</td>
<td>23 (28)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>24 (29)</td>
<td>14 (17)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>23 (28)</td>
<td>19 (23)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>22 (26)</td>
<td>14 (17)</td>
</tr>
<tr>
<td>Palmar-plantar erythrodysesthesia</td>
<td>19 (23)</td>
<td>14 (17)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>18 (22)</td>
<td>16 (19)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>18 (22)</td>
<td>15 (18)</td>
</tr>
</tbody>
</table>

Neste local foram obtidas em janeiro de 1985 as amostras de solo que permitiram obter a rapamicina, substância que inaugurou uma nova era para os pacientes submetidos a transplantes de órgãos.

Homenagem aos investigadores brasileiros.
Novembro de 2000.

Wyeth Brasil.
Island of Rapa Nui

Photo from NASA
RADIANT-3: Study Design

Patients with advanced pNETs (N=410)
- Grade 1 or 2 histology
- Radiologic PD within 12 months
- Prior therapy allowed
- WHO PS ≤ 2

Stratified by:
- WHO PS
- Prior chemotherapy

Everolimus 10 mg daily
(N = 207)

Placebo
(N = 203)

Double blind phase
Primary analysis

Open-label everolimus at progression and unblinding

PD
RADIANT-3: Everolimus for Advanced Pancreatic Neuroendocrine Tumors

Kaplan-Meier median PFS
Everolimus: 11.0 months
Placebo: 4.6 months

HR = 0.35; 95% CI [0.27-0.45]  
$P < .001$

Patients with advanced Lung and GI NETs (N=302)
- Grade 1 or 2 histology
- Radiologic PD
- No syndrome
- Prior therapy allowed
- WHO PS ≤ 1

2:1

Randomized

Everolimus 10 mg qday
(N = 205)

Placebo
(N = 97)

Double blind phase
Primary analysis

Everolimus 10 mg qday

Open-label everolimus if PFS advantage confirmed by DMSC

Real time central radiology review
RADIANT-4: Everolimus for Advanced Neuroendocrine Tumors of the Lung or GI Tract

Kaplan-Meier median PFS
Everolimus: 11.0 months (95% CI, 9.2-13.3)
Placebo: 3.9 months (95% CI, 3.6-7.4)
HR = 0.48 (95% CI, 0.35-0.67); P<.00001

### RADIANT-4: Activity in Less Favorable Subgroups

<table>
<thead>
<tr>
<th>Tumor grading</th>
<th>No.</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>194</td>
<td>0.57 (0.39-0.84)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>107</td>
<td>0.49 (0.29-0.83)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment naive*</th>
<th>No.</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>117</td>
<td>0.65 (0.39-1.08)</td>
</tr>
<tr>
<td>No</td>
<td>185</td>
<td>0.51 (0.35-0.76)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prior chemotherapy</th>
<th>No.</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>77</td>
<td>0.35 (0.19-0.64)</td>
</tr>
<tr>
<td>No</td>
<td>225</td>
<td>0.60 (0.42-0.86)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Baseline CgA</th>
<th>No.</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;2xULN</td>
<td>139</td>
<td>0.40 (0.25-0.62)</td>
</tr>
<tr>
<td>≤2xULN</td>
<td>138</td>
<td>0.70 (0.45-1.11)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Liver Tumor Burden</th>
<th>No.</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>48</td>
<td>0.49 (0.20-1.20)</td>
</tr>
<tr>
<td>≤10%</td>
<td>180</td>
<td>0.67 (0.45-1.00)</td>
</tr>
<tr>
<td>&gt;10%-25%</td>
<td>37</td>
<td>0.62 (0.20-1.93)</td>
</tr>
<tr>
<td>&gt;25%</td>
<td>35</td>
<td>0.18 (0.06-0.50)</td>
</tr>
</tbody>
</table>

## RADIANT-4: Safety

<table>
<thead>
<tr>
<th>Drug-related adverse events</th>
<th>All grades</th>
<th>Grade 3/4</th>
<th>All grades</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Everolimus</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N = 202</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stomatitis*</td>
<td>63%</td>
<td>9%</td>
<td>19%</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>31%</td>
<td>7%</td>
<td>16%</td>
<td>2%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>31%</td>
<td>3%</td>
<td>24%</td>
<td>1%</td>
</tr>
<tr>
<td>Infections†</td>
<td>29%</td>
<td>7%</td>
<td>4%</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>27%</td>
<td>1%</td>
<td>8%</td>
<td>0</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>26%</td>
<td>2%</td>
<td>4%</td>
<td>1%</td>
</tr>
<tr>
<td>Nausea</td>
<td>17%</td>
<td>1%</td>
<td>10%</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>16%</td>
<td>4%</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>16%</td>
<td>1%</td>
<td>6%</td>
<td>0</td>
</tr>
<tr>
<td>Asthenia</td>
<td>16%</td>
<td>1%</td>
<td>5%</td>
<td>0</td>
</tr>
<tr>
<td>Noninfectious pneumonitis‡</td>
<td>16%</td>
<td>1%</td>
<td>1%</td>
<td>0</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>15%</td>
<td>1%</td>
<td>4%</td>
<td>0</td>
</tr>
<tr>
<td><strong>Placebo</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N = 98</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stomatitis*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral edema</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthenia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Noninfectious pneumonitis‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysgeusia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Presented are drug-related adverse events in ≥15% of patients (safety set)

*Includes stomatitis, aphthous stomatitis, mouth ulceration, and tongue ulceration

†Includes all infections

‡Includes pneumonitis, interstitial lung disease, lung infiltration, and pulmonary fibrosis

RADIANT-4 QoL: Time to Definitive Deterioration
≥ 7 points on the FACT-G total score

Everolimus

Placebo

Prevention of Everolimus Stomatitis Using a Dexamethasone-Based Mouthwash (SWISH Trial)

RADIANT-3 Asian subgroup

Patients

- Patients with advanced, PNET (N = 410)
  - Disease progression within 12 months
  - Measurable disease (RECIST 1.0)
  - Prior antitumor therapy allowed

Randomize

Core study

- Everolimus 10 mg/day
  - N = 207

- Placebo
  - N = 203

Asian subgroup

- Everolimus 10 mg/day
  - N = 38

- Placebo
  - N = 31

Treated until PD, intolerable AE, or consent withdrawal

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

Stratified by:
- Prior chemotherapy
- WHO PS 0 vs 1-2

AE, adverse event; PNET, pancreatic neuroendocrine tumors; OS, overall survival; PFS, progression-free survival; PD, progressive disease; WHO PS, World Health Organization performance status

RADIANT-3 Asian subgroup: Progression-free survival

Hazard Ratio = 0.34
95% CI [0.17, 0.69]
Kaplan-Meier medians
Everolimus 10 mg: 14.09 months
Placebo: 6.37 months

No of patients still at risk

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Everolimus</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>38</td>
<td>31</td>
</tr>
<tr>
<td>2</td>
<td>36</td>
<td>28</td>
</tr>
<tr>
<td>4</td>
<td>30</td>
<td>14</td>
</tr>
<tr>
<td>6</td>
<td>27</td>
<td>13</td>
</tr>
<tr>
<td>8</td>
<td>26</td>
<td>12</td>
</tr>
<tr>
<td>10</td>
<td>19</td>
<td>7</td>
</tr>
<tr>
<td>12</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td>14</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>16</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>18</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>20</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>22</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>24</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

HR: Hazard ratio, n, number of patients with response; N, number of patients randomized
RADIANT-4 East Asian Subgroup

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

**Endpoints:**
- **Primary:** PFS (central)
- **Key Secondary:** OS
- **Secondary:** ORR, DCR, safety, HRQoL (FACT-G), WHO PS, NSE/CgA, PK

**Core study**
- Everolimus 10 mg/day
  - N = 205
- Placebo
  - N = 97

**Asian subgroup**
- Everolimus 10 mg/day
  - N = 28
- Placebo
  - N = 18

Treated until PD, intolerable AE, or consent withdrawal

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

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

East Asian subgroup: Patients enrolled from China, Japan, Korea, Taiwan and Thailand were included

Yao JC et al, JSMO 2016
RADIANT-4 East Asian subgroup: Progression-free survival, central radiology review

Hazard Ratio = 0.18 (0.09-0.38)
Kaplan-Meier medians
Everolimus 10 mg: 11.2 (7.3-NA) months
Placebo: 3.1 (1.8-3.7) months

Yao JC et al, JSMO 2016
### Everolimus in the East Asian subgroup: RADIANT -3 and -4 studies

<table>
<thead>
<tr>
<th>Study Description</th>
<th>Overall population</th>
<th>East Asian subgroup</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Everolimus</td>
<td>Placebo</td>
</tr>
<tr>
<td><strong>RADIANT-3 (Advanced Progressive PNET)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median PFS (95% CI), months</td>
<td>11.0 (8.4-13.9)</td>
<td>4.6 (3.1-5.4)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.35 (0.27-0.45)</td>
<td></td>
</tr>
<tr>
<td><strong>RADIANT-4 (Advanced Progressive Non-functional GI and Lung NET)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median PFS (95% CI), months</td>
<td>11.0 (9.23-13.31)</td>
<td>3.9 (3.58-7.43)</td>
</tr>
<tr>
<td>HR (95% CI), p-value</td>
<td>0.48 (0.35-0.67)</td>
<td></td>
</tr>
</tbody>
</table>

CI, confidence interval; GI, gastrointestinal; NET, neuroendocrine tumors; PNET, pancreatic NET; PFS, progression-free survival; HR, hazard ratio

Yao JC et al, JSMO 2016
ALLIANCE 021202 (CALGB 81103): RP2 of Pazopanib vs. placebo in advanced carcinoid (Bergsland)

1:1 Randomized

Patients with advanced carcinoid (N=165)
- PD within 12 months
- Functional or non-functional
- Grade 1 or 2 histology
- Concurrent octreotide allowed if PD documented

Phase 2 accrual completed

Pazopanib 800 mg po daily

Placebo

Crossover to Pazopanib at PD

Real time central radiology review

Activated 6/2013; accrual 107 as of 3/5/2015

Ongoing study
E2211 Study Schema

- **Temozolomide 200 mg/m² po QD days 1-5**
- **Capecitabine 750 mg/m² po BID days 1-14**
- **Temozolomide 200 mg/m² QD days 10-14**

**Phase 2 accrual completed**

- **G1 / G2 advanced pNETs**
- **N = 144**

Stratified by: Prior everolimus, sunitinib, concurrent octreotide
Cell cycle dysregulation in NETs

- Alterations in MEN1, p27, p18, p16 suggest cell cycle dysregulation in NET
- Phase II study of CDK 4/6 inhibitor, ribociclib MDACC completed accrual
- Combination in development
Targeting somatostatin receptor beyond PROMID, CLARINET, and NETTER-1

• Somatostatin Antagonists
  – 68Ga-DOTA-JR11 and 177Lu-DOTA-JR11

• PEN-221 – Phase 1/2a

  SSTR2 Ligand
  ▪ Selective Peptide
  ▪ High affinity

  Linker Chemistry
  ▪ Cleavable
  ▪ Optimized

  DM1 Cytotoxic Payload
  ▪ Potent
  ▪ Clinically proven
Role of immunotherapy in NET

• PD1, PDL1, CTLA-4, Novel combinations
  – Anecdotal experiences and small studies in progress
  – Rigorous data on response rate and PFS in various NET subgroups lacking
Phase II study of PDR001 in patients with NET of pancreatic, GI or thoracic Origin

Progression documented within 6 months of study entry

Patients:
- Advanced, non-functional NET of pancreatic or GI origin (grade 1 or 2) or thoracic (typical or atypical) origin
- Well-Differentiated
- Prior treatment required with everolimus in lung and GI NETs. Prior sunitinib and/or everolimus required in pNET.
- ECOG status 0-2
- Measurable disease as per RECIST 1.1

Total (N=90)*
- GI Cohort (n=30)
- Pancreatic Cohort (n=30)
- Thoracic Cohort (n=30)

*Target enrollment from February 2017

PDR001 400 mg Q4W, flat dose until:
- Confirmed PD per RECIST 1.1
- Toxicity
- Patient withdrawal
No dose modifications allowed
Dose may be interrupted for up to 12 weeks

Futility Interim Analysis:
~ 30 patients with 6 months follow-up
## Improvement in OS for NET patients

<table>
<thead>
<tr>
<th></th>
<th>Total SEER 18 NET cohort (N=14757)</th>
<th>Distant GI NET (N=2681)</th>
<th>Distant pancreatic NET (N=850)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
<td>HR</td>
</tr>
<tr>
<td><strong>2000-2004</strong></td>
<td>1</td>
<td>Reference</td>
<td>1</td>
</tr>
<tr>
<td><strong>2005-2008</strong></td>
<td>0.83</td>
<td>0.78</td>
<td>0.89</td>
</tr>
<tr>
<td><strong>2009-2012</strong></td>
<td>0.79</td>
<td>0.73</td>
<td>0.85</td>
</tr>
</tbody>
</table>

From multivariate Cox model, covariates include time periods, age, race, stage, grade and primary site. P < 0.001 in each comparison.

Dasari et al, JAMA Oncology, In Press 2017
Overall survival among patient with G1/2 distant metastatic NET

Dasari et al, JAMA Oncology, In Press 2017