Recent Clinical Trials and Implications for Therapy of Neuroendocrine Tumors

Matthew Kulke, MD
Director, Dana-Farber/Brigham and Women’s Carcinoid and Neuroendocrine Tumor Program
Associate Professor, Harvard Medical School
Department of Medical Oncology
Dana-Farber Cancer Institute

Metastatic Neuroendocrine Tumors: What are the Treatment Options?

- Somatostatin analogs
- Treatment of Liver Metastases
- Cytotoxic Chemotherapy
- “Targeted” Therapies
Carcinoid Syndrome

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

Flushing associated with carcinoid syndrome

Carcinoid Heart Disease: Tricuspid valve is fibrotic and leaflets retracted

Telotristat Etiprate

A Tryptophan Hydroxylase (TPH) Inhibitor

- Telotristat etiprate is a novel oral inhibitor of TPH, the rate-limiting enzyme in serotonin biosynthesis
- Two early-stage clinical studies demonstrated the safety and evidence of clinical activity in carcinoid syndrome
- Both preclinical and clinical studies suggested that telotristat etiprate is associated with minimal CNS activity
- Granted Fast Track Status and Orphan Drug Designation

Serotonin Synthesis in Carcinoid Tumor Cells

5-HIAA, 5-hydroxyindoleacetic acid; 5-HT, serotonin; 5-HTP, hydroxytryptophan; CNS, central nervous system; TPH, tryptophan hydroxylase

**TELESTAR**

**Phase 3 Study Design**

*Kulke et al, presented at ECCO/ESMO, 2015

1:1:1

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

Run in: Evaluation of bowel movement (BM) frequency

Placebo TID (n=45)

Telotristat etiprate 250 mg TID (n=45)

Telotristat etiprate 500 mg TID* (n=45)

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

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

*Including a blinded titration step of one week of 250 mg TID.

BM, bowel movement; SSA, somatostatin analog; TID, three times daily.


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**TELESTAR: Reduction in Daily Bowel Movement Frequency Averaged Over Double-Blind Treatment Phase**

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

BM, bowel movement.
**TELESTAR**

Proportion of Patients with Durable Response

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=45)</th>
<th>Telotristat etiprate 250 mg (n=45)</th>
<th>Telotristat etiprate 500 mg (n=45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Odds ratio, telotristat etiprate to placebo (95% CI)</td>
<td>–</td>
<td>3.49 (1.33–9.16)</td>
<td>3.11 (1.20–8.10)</td>
</tr>
<tr>
<td>P value</td>
<td>0.011</td>
<td>0.020</td>
<td></td>
</tr>
</tbody>
</table>

All patients continue SSA therapy throughout study period.

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

- Wilcoxon rank-sum test showed significant differences for each telotristat etiprate dose vs. placebo (p<0.001)
- Baseline 5-HIAA levels across treatment arms ranged from 80.96-92.65 mg/24 h

All patients continue SSA therapy throughout study period. Data include only patients for whom both baseline and Week 12 assessments were available.
Expression of SSTR 1, 2A, 2B, 3, 4 and 5 in Pulmonary NET

(Tsuta et al, Path Res Pract 2012; 208: 470-4)

Somatostatin receptors signaling pathways

(Colao et al, Endocrine Rev 2011; 32: 247-71)

Octreotide and Lanreotide for the Treatment of Advanced NET


2015 NCCN Guidelines: Role of SSAs in Advanced Carcinoid Tumor

2015 NCCN Guidelines: Role of SSAs in Advanced Pancreatic NET
Streptozocin-based Therapy for Pancreatic NET

- Streptozocin approved for pancreatic NET in 1982
- Streptozocin/doxorubicin associated with survival benefit compared to streptozocin/5-FU (2.2 vs. 1.5 years)
- Response rates 30-40% in retrospective series

![Graph showing disease progression](image)


Temozolomide-Based Therapy in Pancreatic NET

<table>
<thead>
<tr>
<th>Regimen</th>
<th>N</th>
<th>Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Retrospective Series</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tem (single agent)</td>
<td>12</td>
<td>8%</td>
</tr>
<tr>
<td>Tem/capecitabine</td>
<td>30</td>
<td>70%</td>
</tr>
<tr>
<td>Tem (various)</td>
<td>53</td>
<td>34%</td>
</tr>
<tr>
<td><strong>Prospective Trials</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tem/Thalidomide</td>
<td>11</td>
<td>45%</td>
</tr>
<tr>
<td>Tem/Everolimus</td>
<td>40</td>
<td>40%</td>
</tr>
<tr>
<td>Tem/Bevacizumab</td>
<td>15</td>
<td>33%</td>
</tr>
<tr>
<td>Tem/Bevacizumab</td>
<td>15</td>
<td>64%</td>
</tr>
</tbody>
</table>

E2211: A Randomized Study of Temozolomide or Temozolomide+Capecitabine in Patients with Advanced, Metastatic Pancreatic Neuroendocrine Tumors

PI: Pam Kunz, Activated

Arm 1: Temozolomide 200 mg/m2/day d1-5
28 day cycle; N=69

Arm 2: Capecitabine 750 mg/m2 BID d 1-14
Temozolomide 200 mg/m2 d 10-14
28 day cycle; N=69

Primary Endpoint: PFS

Advanced pNET; prior treatments allowed (no prior temozolomide)
Correlates: MGMT IHC, promoter methylation

Targeting the VEGF Pathway in Neuroendocrine Tumors

Bevacizumab → VEGF
Sunitinib, Sorafenib, Pazopanib → VEGF Receptor
Angiogenesis and Tumor Growth
Phase III, Randomized, Double-Blind Study of Sunitinib vs. Placebo in Patients with Advanced, Progressive, Well-Differentiated Pancreatic Neuroendocrine Tumors

Key Eligibility criteria
- Well-differentiated, malignant pancreatic endocrine tumor
- Disease progression in past 12 months

N=340 (planned)
N=171 (enrolled)

Randomization

Arm A
Sunitinib 37.5 mg/day orally, continuous daily dosing (CDD)*

Arm B
Placebo*

Primary endpoint: PFS

After trial closure patients became candidates for open-label sunitinib in trial NCT00443534 or NCT00428220

Sunitinib in Pancreatic NET: Investigator-Assessed Progression-Free Survival

<table>
<thead>
<tr>
<th></th>
<th>Median PFS</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sunitinib</td>
<td>11.4 months (95% CI 7.4, 19.8)</td>
<td>0.418 (95% CI 0.263, 0.662)</td>
</tr>
<tr>
<td>Placebo</td>
<td>5.5 months (95% CI 3.6, 7.4)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

RADIANT-3: Everolimus vs. Placebo in Advanced Pancreatic NET

Randomization Aug. 2007 – May. 2009

*concurrent somatostatin analogs allowed

RADIANT 3: Investigator-Assessed Progression-Free Survival

Kaplan Meier median PFS
Everolimus: 11.04 months
Placebo: 4.60 months

HR: 0.35 (95% CI [0.27,0.45])
p-value: <0.0001

Streptozocin/5FU vs Doxorubicin/5FU in Advanced Carcinoid (E 1281)

- Streptozocin/5FU
  - PFS: 5.3 mos
  - Response Rate: 16%
  - Renal Toxicity: 34.5%

- Doxorubicin/5FU
  - PFS: 4.5 mos
  - Response Rate: 15.9%

Overall Survival Probability

Sun et al, J Clin Oncol 2005; 23: 4897-4904
**RADIANT 2: PFS by Central Review**

Kaplan-Meier median PFS
- Everolimus + Octreotide LAR: 16.4 months
- Placebo + Octreotide LAR: 11.3 months

Hazard ratio = 0.77; 95% CI [0.59–1.00]

*P*-value = 0.026

![Graph showing Kaplan-Meier median PFS](https://example.com/graph.png)

No. of patients still at risk

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>E + O</th>
<th>P + O</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>216</td>
<td>213</td>
</tr>
<tr>
<td>2</td>
<td>202</td>
<td>202</td>
</tr>
<tr>
<td>4</td>
<td>167</td>
<td>155</td>
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<td>6</td>
<td>129</td>
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<td>8</td>
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<td>0</td>
</tr>
<tr>
<td>38</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* Independent adjudicated central review committee
- *P*-value is obtained from the one-sided log rank test
- Hazard ratio is obtained from unadjusted Cox model

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**2015 NCCN Guidelines: Systemic Options for Advanced Carcinoid Tumor**

![Management of locoregional unresectable disease and/or distant metastases](https://example.com/guidelines.png)

- If complete resection possible:
  - Resect primary + metastases

- Asymptomatic, low tumor burden:
  - Imaging: Multiphasic CT or MRI
  - Consider somatostatin scintigraphy
  - Consider 24-hour urine 5-HIAA, if not already done
  - Consider chromogranin A

- Clinically significant progressive disease:
  - Consider everolimus (10 mg/d) (category 3)
  - Consider interferon alfa-2b (category 3)
  - Consider cytotoxic chemotherapy (category 3), if no other options feasible
**RADIANT-4 Study Design**

*Yao et al, presented at ECCO/ESMO, 2015*

**Randomize 2:1**

**RADIANT-4: PFS by Central Review**

Kaplan–Meier medians

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

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

**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 (worst 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.

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- **Placebo**
  - Stratum A (better prognosis)
  - Lung, stomach, rectum, colon except caecum
  - Treated until PD, intolerable AE, or consent withdrawal

- **Everolimus 10 mg/day**
  - Stratum B (worst prognosis)
  - N=205
  - Treated until PD, intolerable AE, or consent withdrawal

- **Placebo**
  - N=97
  - Patients with well-differentiated (G1/G2), advanced, progressive, nonfunctional NET of lung or GI origin (N=302)
  - Absence of active or any history of carcinoid syndrome
  - Pathologically confirmed advanced disease
  - Radiologic disease progression in ≤ 6 months

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

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

*  Yao et al, presented at ECCO/ESMO, 2015

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- **Placebo**
  - Absence of active or any history of carcinoid syndrome
  - Pathologically confirmed advanced disease
  - Radiologic disease progression in ≤ 6 months

- **Everolimus 10 mg/day**
  - Treated until PD, intolerable AE, or consent withdrawal

**CI, confidence interval; HR, hazard ratio.**
Peptide Receptor Radionuclide Therapy (PRRT)

**NETTER-1: Phase III Study of** $^{177}$Lu-DOTA,Tyr$^3$-Octreotate vs. Octreotide LAR in Patients with Inoperable, Progressive, Somatostatin Receptor Positive Midgut Carcinoid Tumors

*Presented at ECCO/ESMO 2015*

- **200 Patients with Midgut Carcinoid**
- **$^{177}$Lu-DOTA-Tyr$^3$-Octreotate:**
  - 4 administrations of 200 mCi every 8-16 weeks
- **High-dose Octreotide LAR:** 60 mg IM every 4 weeks

**Primary endpoint:** Progression-Free Survival

**Secondary endpoints:** Response rate, TTP, Overall Survival
**NETTER-1: Progression-Free Survival**

Median PFS 8.4 mos vs. not reached (P<0.0001)

**S0518: Study design**

**Study population**
- Advanced G1/2 NET with poor prognosis
  - Progressive disease
  - Refractory syndrome
  - G2 with 6+ lesion
  - Colorectal or gastric primary

**Randomize**

Bevacizumab 15 mg/kg q21 d
octreotide LAR 20 mg q21 d

1:1 Treatment until disease progression

Interferon α-2b 5 mu 3 d/wk
octreotide LAR 20 mg q21 d

**Multiphasic CT or MRI performed every 9 wks**

**Primary endpoint:**
- PFS (Central radiology review)

**Stratification factors:**
- Primary site: Midgut vs others
- RECIST PD since diagnosis
- Histologic grade: G1 vs G2
- Octreotide 2 months prior to registration

Yao et al, ASCO 2015
S0518: PFS by central review

<table>
<thead>
<tr>
<th>Treatment arm</th>
<th>N</th>
<th>Events</th>
<th>Median PFS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab + octreotide LAR</td>
<td>20</td>
<td>0</td>
<td>16.6 (95% CI: 12.9 – 19.6)</td>
</tr>
<tr>
<td>Interferon + octreotide LAR</td>
<td>20</td>
<td>2</td>
<td>15.4 (95% CI: 9.6 – 18.6)</td>
</tr>
</tbody>
</table>

HR 0.93; 95% CI 0.73-1.18; P=0.55

Yao et al, ASCO 2015

Alliance/CALGB 81103: Randomized Phase II Study of Pazopanib or Placebo in Patients with Advanced Carcinoid

**PI: Emily Bergsland, Activated**

**Require:**
- PD within 12 mos

**Stratify:**
- Concurrent octreotide
- PS

**Randomize**

Arm 1: Pazopanib 800 mg po qd

Arm 2: Placebo

Primary Endpoint: PFS

Crossover at progression

150 pts
Receptor Tyrosine Kinase/ AKT/ mTOR Pathway in NET

Active Drugs in NET
- Bevacizumab
- Sunitinib
- Sorafenib
- Pazopanib
- Axitinib
- Temsirolimus
- Everolimus

Cell Growth & Survival

Multicenter Phase II Study of Temsirolimus + Bevacizumab in Advanced Pancreatic NET

- 56 patients with advanced pancreatic NET
- Received temsirolimus 25 mg IV weekly + bev 10 mg/kg q 2 wks
- Partial response rate 41%

Hobday et al, J Clin Oncol 2014 (epub ahead of print)
CALGB 80701: Schema

Key inclusion criteria:
• Advanced pancreatic NET
• Progression within 12 months
• No prior bevacizumab or mTOR inhibitor
• Prior treatment with SSA allowed

Randomize 1:1

Everolimus 10 mg po qd
(Octreotide LAR, institutional standard)
(Treatment until disease progression)

Everolimus 10 mg po qd
Bevacizumab 10 mg/kg IV q 2 weeks
(Octreotide LAR, institutional standard)

Stratification factors:
• Prior SSA
• Prior cytotoxic chemotherapy
• Prior sunitinib

CALGB 80701: Progression-Free Survival by Treatment Arm (Investigator-Assessed)

<table>
<thead>
<tr>
<th>Arm</th>
<th>N (Events)</th>
<th>Median (95% CI)</th>
<th>HR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Everolimus</td>
<td>75 (57)</td>
<td>14.0 (9.1-16.9)</td>
<td>0.80 (0.55-1.17)</td>
<td>.12</td>
</tr>
<tr>
<td>Everolimus + Bev</td>
<td>75 (59)</td>
<td>16.7 (12.6-19.7)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

0 20 40 60 80 100 % Event Free
0 6 12 18 24 30 36 42 Time (Months)
## CALGB 80701: Efficacy Summary

<table>
<thead>
<tr>
<th></th>
<th>Everolimus (n=75)</th>
<th>Everolimus + Bev (n=75)</th>
<th>Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Response Rate</td>
<td>12%</td>
<td>31%</td>
<td>P=0.005</td>
</tr>
<tr>
<td>Median Progression-Free</td>
<td>14.0 mos</td>
<td>16.7 mos</td>
<td>HR 0.80 (95% CI 0.55-1.17)</td>
</tr>
<tr>
<td>Survival</td>
<td></td>
<td></td>
<td>P=0.12*</td>
</tr>
<tr>
<td>Median Overall Survival</td>
<td>35.0 mos</td>
<td>36.7 mos</td>
<td>HR 0.72 (95% CI 0.40-1.28)</td>
</tr>
<tr>
<td>Median Time To Treatment</td>
<td>12.2 mos</td>
<td>12.6 mos</td>
<td>HR 0.95 (95% CI 0.66-1.37)</td>
</tr>
<tr>
<td>Failure</td>
<td></td>
<td></td>
<td>P=0.39</td>
</tr>
</tbody>
</table>

*Primary endpoint was PFS; potential superiority of everolimus + bevacizumab was assessed using a stratified log-rank test with 90% power (1-sided alpha=0.15 to detect a HR of 0.64)

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## Genomic Profiling of Pancreatic NETs

**Table 1. Comparison of commonly mutated genes in PanNETs and PDAC, based on 68 PanNETs and 114 PDACs.**

<table>
<thead>
<tr>
<th>Genes†</th>
<th>PanNET</th>
<th>PDAC‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEN1</td>
<td>44%</td>
<td>0%</td>
</tr>
<tr>
<td>DAAX, ATRX</td>
<td>43%</td>
<td>0%</td>
</tr>
<tr>
<td>Genes in mTOR pathway</td>
<td>15%</td>
<td>0.80%</td>
</tr>
<tr>
<td>TP53</td>
<td>3%</td>
<td>85%</td>
</tr>
<tr>
<td>KRAS</td>
<td>0%</td>
<td>100%</td>
</tr>
<tr>
<td>CDKN2A</td>
<td>0%</td>
<td>25%</td>
</tr>
<tr>
<td>TGFBRI, SMAD3, SMAD4</td>
<td>0%</td>
<td>38%</td>
</tr>
</tbody>
</table>

*Includes point mutations and indels.  †Data from Jones et al., Science 321, 1801 (2008).  

Jiao et al, Science 2011; 331: 1199-203
Mutations in Chromatin-Remodeling Genes in Pulmonary Neuroendocrine Tumors (N=44)

Fernandez-Cuesta et al, Nat Commun 2014; 5: 3518

Somatic Mutation of CDKN1 in Small Intestine Carcinoid Tumors

- Profiled 55 tumors from 50 individuals using combination of whole genome and exome sequencing
- 5/50 individuals had mutations in CDKN1B
- Targeted sequencing in additional cases revealed overall incidence of CDKN1B mutations of 8% (14/180)

Francis et al, Nature Genetics 2013

Mutational analysis of 31 primary and 19 metastatic small intestine NETs: schematic representation of frameshift mutations in CDKN1B
NETS: Multiple Treatment Options

- Symptoms of Hormone Secretion:
  - SSA (octreotide, lanreotide)
  - Telotristat (?)

- Tumor Control (liver predominant disease)
  - Liver directed therapies

- Tumor Control (Systemic)

  Pancreatic NET  |  Carcinoid
  SSA (octreotide, lanreotide)  |  SSA (octreotide, lanreotide)
  Everolimus  |  Everolimus
  Sunitinib  |  PRRT
  Temozolomide

- Future studies: combination therapy, molecular and genetic predictors of response, novel targets and agents