Recent Advances in Neuroendocrine Tumors: Diagnostics and Therapeutics

Manisha H. Shah, M.D.
Professor of Internal Medicine
The Ohio State University
Comprehensive Cancer Center

manisha.shah@osumc.edu
Acknowledgements

Following Endocrine Medical Oncology faculty contributed to preparing this power point presentation.

• Allan Espinosa
• Bhavana Konda
• Manisha H. Shah
Disclosures

• Advisory board honorarium from Eisai and Loxo.

• Research funding for clinical trials from Eisai, Loxo and Merk & Co.
Objectives

- Understand Recent Advances in **Diagnostics** of Neuroendocrine Tumors
- Understand recent advances in **Therapeutics** of Neuroendocrine Tumors
  - Carcinoid syndrome
  - Tumor management
- Understand benefits/risks of therapeutics
Outline

• Introduction
• Carcinoid syndrome
• Systemic therapies to target tumors
• Advances in diagnostics
• Take-home messages
Introduction: Spectrum of NET

Least aggressive = Grade 1 NET

Carcinoid tumor
Pancreatic NET
Pheochromocytoma
Paraganglioma
Medullary thyroid cancer
Atypical carcinoid tumor

Most aggressive = Grade 3 NEC

Melanoma
Small Cell Carcinoma
Merkel Cell Carcinoma

Grade 2 NET
Neuroendocrine Tumors (NET) WHO Classification

Grade 1 NET
- Ki-67 <3%
- Mitosis <2/10 HPF

Grade 2 NET
- Ki-67 3-20%
- Mitosis 2-20/10 HPF

Grade 3 NEC
- Ki-67 >20%
- Mitosis >20/10 HPF
Increasing incidence of NET: 1973-2012

• The annual age-adjusted incidence of NETs per 100,000 persons
  – 1.09 in 1973
  – 6.98 in 2012

• Increased incidence across all sites, stages, grades of NET

• Related to early detection (use of imaging/endoscopy)

Dasari et al. JAMA Oncology, April 2017
Median Survival of NET by Grade of Differentiation

Grade 1 NET (10 yrs)
Grade 2 NET (5 yrs)
Grade 3 NEC (10 mths)

Yao et al, J Clin Oncol, 2008
Carcinoid Syndrome

(Tumor cell)

Tryptophan

↓ Tryptophan hydroxylase

5-Hydroxy Tryptophan

↓ Aromatic L-amino acid decarboxylase

Serotonin

Serotonin (Blood)

↓

5-Hydroxyindolacetic acid /5-HIAA (Urine)
Carcinoid Syndrome

- Flushing (85-90%): prostaglandins, histamine, kallikrein, 5-hydroxytryptophan (5-HTP), substance P
- Diarrhea (70-80%): serotonin, prostaglandins, histamine
- Bronchospasm (10-20%): histamine, 5-HTP
- Venous telangiectasia (25%): unknown
- Carcinoid heart disease (50%): serotonin
- Pellagra (5%): niacin deficiency

Carcinoid Syndrome: Management

1. Somatostatin analogs
   - Octreotide SQ 100-500 mcg TID
   - Octreotide LAR 20-60 mg every 4 weeks
   - Octreotide SQ infusion (pump) 30-80 mcg/hr
   - Lanreotide 60-120 mg SQ every 4 weeks

2. Telotristat ethyl
   - Novel oral therapy
   - 250-500 mg PO TID

3. Histamine-1 receptor antagonist
   - Cyproheptadine 4 mg PO TID
Octreotide LAR for Carcinoid syndrome

Prospective multicenter trial with parallel group design N=93

Carcinoid tumor with carcinoid syndrome

Symptoms controlled by SQ Octreotide

Screening Octreotide 300-900 mcg/day (2 weeks)

Primary endpoint:
Treatment response at week 20 & 24

Treatment success: no rescue medication needed at any time point
Partial success: rescue needed ≤2 occasions for ≤5 days
Treatment failure: rescue needed ≥3 occasions/≥5

Rubin et al, JCO 1999 Feb;17(2):600-6
Octreotide LAR in Carcinoid Syndrome

1998: FDA approval of Octreotide LAR for severe diarrhea and flushing from malignant carcinoid syndrome and for profuse watery diarrhea from VIPomas

Rubin et al, JCO 1999 Feb;17(2):600-6
Commentary in American Society of Clinical Oncology (ASCO) Post

Telotristat Ethyl: A Novel Therapy for Carcinoid Syndrome—Not a Panacea but a Step in the Right Direction

By Bhavana Konda, MD, MPH, and Manisha H. Shah, MD
February 10, 2017
Tweet this page

The development of telotristat ethyl for treating carcinoid syndrome represents a step in the right direction for improving the quality of life of these patients.

— Bhavana Konda, MD, MPH (left), and Manisha H. Shah, MD

Feb 2017: Commentary on Telotristat (J Clin Oncol) by Konda and Shah
Telotristat Ethyl and the TELESTAR
International Multicenter Phase III Double-blind Placebo-controlled Trial

- Well differentiated metastatic NET
- Carcinoid syndrome
- ≥4 BM/day
- Stable dose SSA for ≥3 mo

Jan 13 - Mar 15

**Primary endpoint:**
Mean reduction in BM from baseline

**Secondary endpoints:**
Change in week 12 u5HIAA from baseline, no. of flushing episodes, abdominal pain severity

1:1:1

Telotristat Ethyl 500 mg TID
n=45

Telotristat Ethyl 250mg TID
n=45

Placebo
n=45

Double-blind treatment period: 12 wks
Ongoing open label extension: Telotristat Ethyl 500mg TID (N=115) for 36 wks

Kulke et al, JCO. 2017 Jan;35(1):14-23
Results: Response to Telotristat Ethyl

Feb 2017: FDA approval of Telotristat Ethyl in combination with somatostatin analogue therapy for carcinoid syndrome diarrhea

Kulke et al, JCO. 2017 Jan;35(1):14-23
## Results: Adverse Events of Telotristat Ethyl

<table>
<thead>
<tr>
<th>Category</th>
<th>Placebo</th>
<th>Telotristat Ethyl 250 mg TID</th>
<th>Telotristat Ethyl 500 mg TID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>5 (11.1)</td>
<td>6 (13.3)</td>
<td>14 (31.1)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4 (8.9)</td>
<td>2 (4.4)</td>
<td>5 (11.1)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>8 (17.8)</td>
<td>5 (11.1)</td>
<td>10 (22.2)</td>
</tr>
<tr>
<td>Depression-related</td>
<td>3 (6.7)</td>
<td>3 (6.7)</td>
<td>7 (15.6)</td>
</tr>
<tr>
<td>Confusional state</td>
<td>0</td>
<td>0</td>
<td>3 (6.7)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4 (8.9)</td>
<td>4 (8.9)</td>
<td>7 (15.6)</td>
</tr>
<tr>
<td>Increased GGT</td>
<td>0</td>
<td>4 (8.9)</td>
<td>4 (8.9)</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>0</td>
<td>1 (2.2)</td>
<td>3 (6.7)</td>
</tr>
<tr>
<td>Increased Alk phos</td>
<td>0</td>
<td>0</td>
<td>3 (6.7)</td>
</tr>
</tbody>
</table>

# Systemic Therapies for Neuroendocrine Tumors

<table>
<thead>
<tr>
<th>Carcinoid tumors (GI/Lung)</th>
<th>Pancreatic neuroendocrine tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somatostatin analogues</td>
<td>Somatostatin analogues</td>
</tr>
<tr>
<td>- Octreotide</td>
<td>- Octreotide</td>
</tr>
<tr>
<td>- Lanreotide</td>
<td>- Lanreotide</td>
</tr>
<tr>
<td>Everolimus (Feb 2016)</td>
<td>Everolimus (May 2011)</td>
</tr>
<tr>
<td>Telotristat (C.syndrome) (Feb 2017)</td>
<td>Sunitinib (May 2011)</td>
</tr>
<tr>
<td>Peptide Receptor Radionuclide Radionuclide Therapy ((^{177}\text{Lu-Dotatate})) (pending)</td>
<td>Peptide Receptor Radionuclide Therapy ((^{177}\text{Lu-Dotatate}))(pending)</td>
</tr>
<tr>
<td>Capecitabine/Temozolamide</td>
<td></td>
</tr>
</tbody>
</table>
Somatostatin Analogs in Carcinoid Tumors

Pancreatic Neuroendocrine Tumors (pNET)
Placebo-Controlled, Double-Blind, Prospective, Randomized Study on the Effect of Octreotide LAR in the Control of Tumor Growth in Patients With Metastatic Neuroendocrine Midgut Tumors: A Report From the PROMID Study Group

Anja Rinke, Hans-Helge Müller, Carmen Schade-Brittinger, Klaus-Jochen Klose, Peter Barth, Matthias Wied, Christina Mayer, Behnaz Aminossadati, Ulrich-Frank Pape, Michael Blaker, Jan Harder, Christian Arnold, Thomas Gress, and Rudolf Arnold

The NEW ENGLAND JOURNAL of MEDICINE

Lanreotide in Metastatic Enteropancreatic Neuroendocrine Tumors

Martyn E. Caplin, D.M., Marianne Pavel, M.D., Jarosław B. Ćwikła, M.D., Ph.D., Alexandria T. Phan, M.D., Markus Raderer, M.D., Eva Sedláčková, M.D., Guillaume Cadiot, M.D., Ph.D., Edward M. Wolin, M.D., Jaume Capdevila, M.D., Lucy Wall, M.D., Guido Rindi, M.D., Ph.D., Alison Langley, M.Sc., Séverine Martinez, B.Sc., Joëlle Blumberg, M.D., and Philippe Ruszniewski, M.D., Ph.D., for the CLARINET Investigators*
PROMID Trial: Octreotide LAR

Log-rank test stratified by functional activity, p=0.000072, HR=0.34 (95% CI, 0.20 to 0.59)

Rinke et al. JCO. 2009 Oct 1;27(28):4656-63
CLARINET Trial: Lanreotide

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

P<0.001 for the comparison of PFS
HR for progression or death, 0.47 (95% CI, 0.30-0.73)

Caplin et al. NEJM 2014; 371:224-233

FDA approval of Lanreotide for unresectable, well or moderately differentiated, locally advanced or metastatic GEP-NETs in Dec 2014
Everolimus in Pancreatic Neuroendocrine Tumors (pNET) Carcinoid Tumors
**RADIANT-4 Study Design**

*International Multicenter Phase III Double-blind Placebo-controlled Trial*

Progressive advanced non-functional GI or lung NET  
N=302  
Apr 12-Aug 13

**Stratified by:**  
- Prior SSA  
- Tumor origin  
- WHO PS

**Primary endpoint:**  
- Progression free survival

**Secondary endpoints:**  
- OS, Response, disease control, QOL, PS, biomarkers, PK

**Randomize**  
2:1

**Crossover not allowed at time of PD**

**Treatment until PD**

**Placebo + Best supportive care**  
n=97

**Everolimus orally 10 mg/day + Best supportive care**  
n=205

*Multi-phasic CT or MRI every 8 weeks x 12 mo then every 12 weeks*

EVEROLIMUS (RADIANT-4 Trial) in Carcinoid Tumors

Median Progression Free Survival
Everolimus: 11.0 months
Placebo: 3.9 months
HR: 0.48
p<0.00001

EVEROLIMUS (RADIANT-4 Trial) in Carcinoid Tumors: First pre-planned interim analysis

February 2016 FDA approval of Everolimus in progressive non-functioning GI and Lung NETs

Overall Survival

HR: 0.64 (95% CI: 0.40-1.05)  
p=0.037 (boundary for statistical significance was 0.0002)
## Results: Treatment-related Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>Everolimus All grades</th>
<th>Everolimus Grade 1</th>
<th>Everolimus Grade 2</th>
<th>Everolimus Grade 3</th>
<th>Everolimus Grade 4</th>
<th>Placebo All grades</th>
<th>Placebo Grade 1</th>
<th>Placebo Grade 2</th>
<th>Placebo Grade 3</th>
<th>Placebo Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomatitis*</td>
<td>127 (63%)</td>
<td>72 (36%)</td>
<td>37 (18%)</td>
<td>18 (9%)</td>
<td>0</td>
<td>19 (19%)</td>
<td>17 (17%)</td>
<td>2 (2%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>63 (31%)</td>
<td>30 (15%)</td>
<td>18 (9%)</td>
<td>13 (6%)</td>
<td>2 (1%)</td>
<td>16 (16%)</td>
<td>10 (10%)</td>
<td>4 (4%)</td>
<td>2 (2%)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>62 (31%)</td>
<td>35 (17%)</td>
<td>20 (10%)</td>
<td>5 (2%)</td>
<td>2 (1%)</td>
<td>24 (24%)</td>
<td>17 (17%)</td>
<td>6 (6%)</td>
<td>1 (1%)</td>
<td>0</td>
</tr>
<tr>
<td>Infections†</td>
<td>59 (29%)</td>
<td>12 (6%)</td>
<td>33 (16%)</td>
<td>10 (5%)</td>
<td>4 (2%)</td>
<td>4 (4%)</td>
<td>1 (1%)</td>
<td>3 (3%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>55 (27%)</td>
<td>42 (21%)</td>
<td>12 (6%)</td>
<td>1 (&lt;1%)</td>
<td>0</td>
<td>8 (8%)</td>
<td>6 (6%)</td>
<td>2 (2%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Peripheral oedema</td>
<td>52 (26%)</td>
<td>30 (15%)</td>
<td>18 (9%)</td>
<td>4 (2%)</td>
<td>0</td>
<td>4 (4%)</td>
<td>2 (2%)</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>35 (17%)</td>
<td>26 (13%)</td>
<td>6 (3%)</td>
<td>2 (1%)</td>
<td>1 (&lt;1%)</td>
<td>10 (10%)</td>
<td>7 (7%)</td>
<td>3 (3%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Asthenia</td>
<td>33 (16%)</td>
<td>8 (4%)</td>
<td>22 (11%)</td>
<td>2 (1%)</td>
<td>1 (&lt;1%)</td>
<td>5 (5%)</td>
<td>4 (4%)</td>
<td>1 (1%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Anaemia</td>
<td>33 (16%)</td>
<td>5 (2%)</td>
<td>20 (10%)</td>
<td>8 (4%)</td>
<td>0</td>
<td>2 (2%)</td>
<td>0</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
<td>0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>32 (16%)</td>
<td>22 (11%)</td>
<td>9 (4%)</td>
<td>1 (&lt;1%)</td>
<td>0</td>
<td>6 (6%)</td>
<td>2 (2%)</td>
<td>4 (4%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Non-infectious pneumonitis†</td>
<td>32 (16%)</td>
<td>5 (2%)</td>
<td>24 (12%)</td>
<td>3 (1%)</td>
<td>0</td>
<td>1 (1%)</td>
<td>0</td>
<td>1 (1%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>30 (15%)</td>
<td>26 (13%)</td>
<td>3 (1%)</td>
<td>1 (&lt;1%)</td>
<td>0</td>
<td>4 (4%)</td>
<td>4 (4%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>26 (13%)</td>
<td>19 (9%)</td>
<td>6 (3%)</td>
<td>1 (&lt;1%)</td>
<td>0</td>
<td>4 (4%)</td>
<td>4 (4%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cough</td>
<td>26 (13%)</td>
<td>18 (9%)</td>
<td>8 (4%)</td>
<td>0</td>
<td>0</td>
<td>3 (3%)</td>
<td>3 (3%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>22 (11%)</td>
<td>14 (7%)</td>
<td>4 (2%)</td>
<td>2 (1%)</td>
<td>2 (1%)</td>
<td>5 (5%)</td>
<td>4 (4%)</td>
<td>1 (1%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hyperglycaemia</td>
<td>21 (10%)</td>
<td>5 (2%)</td>
<td>9 (4%)</td>
<td>7 (3%)</td>
<td>0</td>
<td>2 (2%)</td>
<td>2 (2%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>21 (10%)</td>
<td>4 (2%)</td>
<td>15 (7%)</td>
<td>2 (1%)</td>
<td>0</td>
<td>4 (4%)</td>
<td>2 (2%)</td>
<td>1 (1%)</td>
<td>0</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

RADIANT-3 Study Design

International Multicenter Phase III Double-blind Placebo-controlled Trial

Pts with progressive advanced pNET N=410
Aug 07-May 09

Stratified by:
- WHO PS
- Prior chemo

Placebo + Best supportive care n=203
Multi-phasic CT or MRI performed every 12 weeks

Randomize
1:1
Crossover allowed at time of PD

Everolimus orally 10 mg/day + Best supportive care n=207

Treatment until PD

Primary endpoint:
- Progression free survival

Secondary endpoints:
- Response, OS, biomarkers, safety & PK

Results: Progression Free Survival

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

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Everolimus (%)</th>
<th>Placebo (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>6</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>8</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>12</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>14</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>16</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>18</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>20</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>22</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>24</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>26</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>28</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>30</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

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

Hazard ratio = 0.35; 95% CI [0.27 - 0.45]
P-value: <0.0001

May 2011: FDA approval of Everolimus in progressive pNETs
Sunitinib in Pancreatic Neuroendocrine Tumors
Sunitinib in pNET

International Multicenter Phase III Double-blind Placebo-controlled Trial

Pts with progressive advanced pNET
N=171
Jun 07-Apr 09

Randomize 1:1

Sunitinib 37.5 mg/day + Best supportive care
n=86

Placebo+
Best supportive care
N=85

Treatment until PD

Tumor imaging at week 5, week 9, and every 8 weeks thereafter

Primary endpoint:
• Progression free survival

Secondary endpoints:
• OS, ORR, time to tumor response, response duration, safety, & patient-reported outcomes

Raymond et al. *NEJM* 2011; 364:501-513
Results: Progression Free Survival

HR 0.42, 95% CI 0.26-0.66, p<0.001

Sunitinib: median PFS=11.4 mo
Placebo: median PFS=5.5 mo

May 2011: FDA approval of Sunitinib in progressive well-differentiated pNETs

Raymond et al. *NEJM* 2011; 364:501-513
Capecitabine/Temozolamide in Pancreatic Neuroendocrine Tumors
CAP-TEM Chemotherapy in pNET

RETROSPECTIVE DATA in pancreatic NET (n=30)

Capecitabine 750 mg/m² BID d 1-14
Temozolamide 200 mg/m² QD d 10-14
28 day cycle

Median Progression Free Survival 18 months
Objective Response Rate 70%

68Ga-DOTATATE PET and PRRT: Background
$^{68}$Ga-DOTATATE PET imaging

Triple phase CT A/P

$^{68}$Ga-DOTATATE PET
<table>
<thead>
<tr>
<th></th>
<th>68Ga-DOTATATE PET/CT</th>
<th>111In-pentetreotide (octreoscan)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sensitivity</strong></td>
<td>96% (86–100)</td>
<td>72% (58–75)</td>
</tr>
<tr>
<td><strong>Specificity</strong></td>
<td>93% (77–99)</td>
<td>93% (77–99)</td>
</tr>
<tr>
<td><strong>PPV</strong></td>
<td>96% (86–100)</td>
<td>95% (82–99)</td>
</tr>
<tr>
<td><strong>NPV</strong></td>
<td>93% (77–99)</td>
<td>65% (48–94)</td>
</tr>
</tbody>
</table>

Jun 2016: FDA approval of 68Ga-DOTATATE (NETSPOT) for PET imaging in Neuroendocrine tumor detection

Prospective study: Gallium PET/CT in NET

Prospective study
N= 191 patients

Imaging: Functional (68Ga-DOTATATE PET/CT, Octreoscan), Anatomic (multiphasic CT scan and/or MRI)

Other tests: comprehensive biochemical testing

Primary outcome measure: detection of lesions by each imaging study

Sadowski et al, J Clin Oncol 34:588-596.
Results: Gallium PET/CT in NET

- % detection of lesions by imaging modality
  - Gallium PET/CT imaging: 95% of lesions
  - Octreoscan SPECT/CT: 31% of lesions
  - Anatomic imaging detected: 45% of lesions

29% Gallium PET found a previously unknown primary tumor

33% had a change in management recommendation

- Patients with carcinoid symptoms but negative biochemical testing, Gallium PET detected lesions in 65% of patients, 40% of which were not detected by other imaging
Peptide Receptor Radionuclide Therapy (PRRT)
PRRT: Background

- **Peptide Receptor Radionuclide Therapy (PRRT)**
  - Systemic radiotherapy
  - Radiolabeled Somatostatin analogs
- **Two potent agents**
  - $^{177}$Lu-[DOTA$^0$,Tyr$^3$]octreotate (DOTATATE)
  - $^{90}$Y-[DOTA$^0$,Tyr$^3$]octreotide (DOTATOC)
- **Availability**
  - Not yet available in US
  - Tested and available in Europe x >15 years
### PRRT: Phase II trial data

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Radiolabeled somatostatin analog</th>
<th>Response (PR+CR)</th>
<th>Symptom relief or reduction</th>
<th>Median overall survival (Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bushnell, 2010 USA</td>
<td>90</td>
<td>90Y-edotretotide</td>
<td>4%</td>
<td>&gt;50%</td>
<td>26.9</td>
</tr>
<tr>
<td>Delpassand, 2008 USA</td>
<td>18</td>
<td>In-111 pentetreotide</td>
<td>11%</td>
<td>N/A</td>
<td>13.3</td>
</tr>
<tr>
<td>Kwekkeboom 2008 Netherlands</td>
<td>310</td>
<td>Lu-177-Dotatate</td>
<td>30%</td>
<td>N/A</td>
<td>46</td>
</tr>
<tr>
<td>Forrer 2006 Switzerland</td>
<td>116</td>
<td>90-Y-Dotatoc</td>
<td>27%</td>
<td>83%</td>
<td>N/A</td>
</tr>
<tr>
<td>Anthony 2002 USA</td>
<td>26</td>
<td>In-111 pentetreotide</td>
<td>8%</td>
<td>62%</td>
<td>18</td>
</tr>
</tbody>
</table>

Schmidt et al, *Oncogene*, 2011
Commentary in American Society of Clinical Oncology (ASCO) Post

Major Breakthrough in Development of Systemic Targeted Therapy for Midgut Neuroendocrine Tumors

By Allan V. Espinosa, MD, and Marisha H. Shah, MD
June 25, 2017
Tweet this page

This issue of The ASCO Post discusses a recent trial reported by Strosberg et al in The New England Journal of Medicine, which was the first phase III randomized international trial evaluating lutetium-177 (177Lu)-Dota-Tate radionuclide therapy in midgut Neuroendocrine Tumors. In this trial, 177Lu-Dota-Tate showed improved response rates compared to somatostatin analogues. Sustained hormonal response and overall survival in this trial are unprecedented for this patient population. Currently, somatostatin analogues are the only approved therapeutic option for patients who have had disease progression on these agents.

Study Background

Jun 2017: Commentary on PRRT (NEJM) by Espinosa and Shah
NETTER-1 Study Design

Multicenter Phase III Trial of PRRT in mid gut NET

- Pts with progressive advanced mid-gut NET
- Ki 67 ≤20%
- Measurable ds
- Somatostatin receptor positive

Randomize 1:1

177Lu--DOTATATE IV plus octreotide LAR 30 mg IM every 8 weeks x 4 followed by octreotide LAR 30mg IM every month
N=116

Octreotide LAR 60 mg IM every 4 weeks
N=113

Response evaluation by RECIST every 12 weeks

Primary endpoint:
• Progression free survival

N=229

Strosberg et al, NEJM 2017. 376:125-35
NETTER-1 Trial: $^{177}$Lu-Dotatate (PRRT) increases median PFS

HR (progression/death): 0.21, p<0.001
Median PFS: $^{177}$Lu- Dotatate: NR
Control: 8.4 months

Strosberg et al, NEJM 2017. 376:125-35
NETTER-1 Trial: Preliminary evidence of an OS benefit with $^{177}\text{Lu}$-Dotatate (PRRT)


HR 0.40, $p=0.004$
**NETTER-1 Trial: $^{177}$Lu-Dotatate (PRRT) results in objective response**

<table>
<thead>
<tr>
<th></th>
<th>$^{177}$Lu Dotatate (n=101)</th>
<th>Octreotide LAR 60 mg (n=100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response</td>
<td>1 (1%)</td>
<td>0</td>
</tr>
<tr>
<td>Partial Response</td>
<td>17 (17%)</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Overall Response</td>
<td>18%</td>
<td>3%</td>
</tr>
<tr>
<td>$p&lt;0.001$</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### NETTER-1 Trial: $^{177}$Lu-Dotatate (PRRT) has good safety profile

<table>
<thead>
<tr>
<th></th>
<th>$^{177}$Lu-Dotatate (N=111)</th>
<th>Control (N=110)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any grade % (grade 3/4 %)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any AE</td>
<td>95 (41)</td>
<td>84 (33)</td>
</tr>
<tr>
<td>Nausea</td>
<td>59 (4)</td>
<td>12 (2)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>47 (7)</td>
<td>10 (1)</td>
</tr>
<tr>
<td>Fatigue/asthenia</td>
<td>40 (2)</td>
<td>25 (2)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>25 (2)</td>
<td>1 (0)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>18 (9)</td>
<td>2 (0)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>18 (0)</td>
<td>8 (3)</td>
</tr>
<tr>
<td>Headache</td>
<td>16 (0)</td>
<td>5 (0)</td>
</tr>
<tr>
<td>Anemia</td>
<td>14 (0)</td>
<td>5 (0)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>10 (1)</td>
<td>1 (0)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>11 (0)</td>
<td>2 (0)</td>
</tr>
</tbody>
</table>

PRRT: Indications for use

Somatostatin receptor positive NETs

- Octreoscan or
- $^{68}$Ga-DOTATATE PET scan (NETSPOT)

Treatment of Carcinoid and pNET

- Progressive metastatic disease
- Widespread nature/extra-hepatic mets
- Before or after medical therapies

Comparison to other systemic therapies

One of the best systemic therapies for carcinoid tumors
- Very effective and easy tolerability

Anticipate FDA approval of $^{177}$Lu-DOTATATE in the coming months
Our patient: Response to PRRT

Pre-therapy
Serum CgA: 120,000

12 wks post-therapy
Serum CgA: 5,000

Index Lesions
10.4 x 7.7 cm
3.8 x 2.8 cm

5.0 x 4.3 cm
3.1 x 2.5 cm
Future Directions: Clinical Trials in NET at OSU

- **OSU 17208**: Expanded access protocol for therapeutic use of $^{177}$Lu-DOTA0-Tyr3-Octreotate in patients with inoperable, somatostatin receptor positive, midgut carcinoid tumors, progressive under somatostatin analogue therapy

- **SWOG 1609 DART**: Dual Anti-CTLA-4 and Anti-PD-1 Blockade In Rare Tumors

- **ECOG 2161**: A Phase II Study of MLN0128 (TAK-228) in Rapalog-Resistant Advanced Pancreatic Neuroendocrine Tumors (PNET)

- **OSU 15075**: Multicenter Phase 2 Study of Nintedanib for Patients with Advanced Carcinoid Tumors
Take-Home Messages

- NET-spectrum of cancers
- Grade of differentiation is KEY
- Multidisciplinary Team
- Multimodality therapies (local, regional, systemic)
- Not all pts with stage IV NEC need treatment at diagnosis
- Incredible progress in the field - 2015-2017: Everolimus in carcinoid tumors, (PRRT) and Gallium PET scan in NET, Telotristat Ethyl for carcinoid syndrome
Thanks for creating a fertile land for NET program at OSU--

Clinical Era
Zollinger-Ellison Syndrome
1955

R.M. Zollinger
E.H. Ellison
Gastrinoma

Edward Martin

Thomas O’dorisio