Treatment Options in NETs; An Overview

By

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Therapeutic Options NETs

**Surgery**
- Curative (rarely), Ablative (very often)

**Debulking**
- Radiofrequency ablation (RFA)
- Embolization/chemoembolization/radioembolization (SIRT)

**Irradiation**
- External (bone, brain-mets)
- Tumor targeted, radioactive therapy (MIBG, Y\(^{90}\)-DOTATOC, Lu\(^{177}\) -DOTATATE)

**Medical therapy**
- Chemotherapy
- Biological treatment:
  - Somatostatin analogs
  - α-interferon
  - m-TOR inhibitors
  - VEGF R inhibitors
  - Other TKI’s
Factors Influencing the Therapeutic Decision

- Type of NET-tumor
- TNM stage and WHO-grade
- Extent of liver involvement
- Functioning vs. non-functioning tumor
- Patients performance status
- Availability of different therapeutic modalities

*NB!* The treatment of most patients is a combination of surgery, PRRT and medical treatment
Medical treatment

**Chemotherapy:**
- Local (chemoembolization)
- Systemic

**Biotherapy:**
- Somatostatin analogs
- α-IFN
- m-TOR inhibition
- VEGF-inhibitors: bevacizumab, sunitinib
- alkylation agent

Sugar moiety
- bone marrow
- facilitates uptake
<table>
<thead>
<tr>
<th>Reference</th>
<th>Type of Tumour</th>
<th>Regimen</th>
<th>No. of Patients</th>
<th>Objective Response (%)</th>
<th>Response duration (months)</th>
<th>Median survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moertel et al</td>
<td>Pancreatic</td>
<td>STZ</td>
<td>42</td>
<td>36</td>
<td>17</td>
<td>16.5</td>
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<td></td>
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<td>STZ + 5-FU</td>
<td>42</td>
<td>63</td>
<td>17</td>
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<td>Eriksson et al</td>
<td>Pancreatic</td>
<td>STZ + 5-FU or DOX</td>
<td>44</td>
<td>45</td>
<td>27.5</td>
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<td>STZ + DOX</td>
<td>36</td>
<td>69</td>
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<td></td>
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<td>STZ + 5-FU</td>
<td>33</td>
<td>45</td>
<td>14</td>
<td>18</td>
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<tr>
<td>Cheng and Saltz</td>
<td>Pancreatic</td>
<td>STZ + DOX</td>
<td>16</td>
<td>6</td>
<td>18</td>
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<td>McCollum et al</td>
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<td>16</td>
<td>6</td>
<td>3.9</td>
<td>20.2</td>
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<td>Kouvaraki et al</td>
<td>Pancreatic</td>
<td>STZ + DOX + 5-FU</td>
<td>84</td>
<td>39</td>
<td>9.3</td>
<td>40</td>
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<td>Moertel and Hanley</td>
<td>Carcinoids</td>
<td>5-FU + cyclophosphamide STZ + 5-FU</td>
<td>47</td>
<td>33</td>
<td>-</td>
<td>-</td>
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<tr>
<td></td>
<td></td>
<td>STZ + 5-FU</td>
<td>42</td>
<td>33</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Engstrom et al</td>
<td>Carcinoids</td>
<td>STZ + 5-FU DOX</td>
<td>80</td>
<td>22</td>
<td>8</td>
<td>16</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>81</td>
<td>21</td>
<td>6.5</td>
<td>12</td>
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<tr>
<td>Bukowski et al</td>
<td>Carcinoids</td>
<td>STZ + DOX + 5-FU + cyclophosphamide STZ + 5-FU</td>
<td>56</td>
<td>31</td>
<td>-</td>
<td>-</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sun et al</td>
<td>Carcinoids</td>
<td>DOX + 5-FU</td>
<td>25</td>
<td>15.9</td>
<td>4.5</td>
<td>15.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>27</td>
<td>16</td>
<td>5.3</td>
<td>24.3</td>
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<td>Moertel et al</td>
<td>Poorly differentiated</td>
<td>Cisplatin + etoposide</td>
<td>18</td>
<td>67</td>
<td>8</td>
<td>19</td>
</tr>
<tr>
<td>Mitry et al</td>
<td>Poorly differentiated</td>
<td>Cisplatin + etoposide</td>
<td>41</td>
<td>42</td>
<td>9</td>
<td>15</td>
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<tr>
<td>Fjallskog et al</td>
<td>Poorly differentiated</td>
<td>Cisplatin + etoposide</td>
<td>36</td>
<td>47</td>
<td>9</td>
<td>-</td>
</tr>
<tr>
<td>Turner et al</td>
<td>Pancreatic</td>
<td>Cisplatin + 5-FU STZ</td>
<td>49</td>
<td>38</td>
<td>9</td>
<td>30</td>
</tr>
</tbody>
</table>
Temozolomide, alkylates DNA-bases (guanin) discovered in 1981

- Oral imidazotetrazine with activity in advanced melanoma and primary brain tumors
- Temozolomide and dacarbazine share the active intermediary MTIC
- Has a high oral bioavailability (100%) and extensive tissue distribution, and rapid penetration through blood-brain barrier, 10-30%, (shown by PET)
Chemotherapy: Temozolomide

Ekeblad; Clin Cancer Res 2007
- 36 patients (35 foregut, 12 EPT, 12 bronchial, 7 thymus)
- median 2.4 prior anti-tumor medical regimen
- **RR 14% (40% in low O^6 MGMT), TTP 7 m.**

Isacoff; ASCO 2006 Abs #14023
- + capecitabine
- 17 patients, failed prior chemotherapy, histology?
- 1 CR, 9 PR (59%), duration 9 months

Kulke; ASCO 2006 Abs # 4044
- + bevacizumab
- 34 patients, 18 EPT, 16 carcinoids
- 12 prior chemotherapy
- EPT; RR 24%. Carcinoids RR 0%
- PFS 8.6 m
Association of MGMT Status with Response to Temozolomide-Based Therapy

<table>
<thead>
<tr>
<th>Immunohistochemical MGMT Status According to Tumor Type</th>
<th>N</th>
<th>MGMT Deficient</th>
<th>MGMT Intact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatic Neuroendocrine</td>
<td>37</td>
<td>19 (51%)</td>
<td>17 (49%)</td>
</tr>
<tr>
<td>Carcinoid</td>
<td>60</td>
<td>0</td>
<td>60 (100%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment Response According to MGMT Status</th>
<th>N</th>
<th>Radiologic Response (RECIST)</th>
<th>Median PFS (mos)</th>
<th>Median OS (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MGMT+</td>
<td>16</td>
<td>0/16 (0%)</td>
<td>9.25</td>
<td>14</td>
</tr>
<tr>
<td>MGMT-</td>
<td>5</td>
<td>4/5 (80%)</td>
<td>19</td>
<td>Not reached</td>
</tr>
</tbody>
</table>

Capecitabin plus Temozolomide in Pancreatic Endocrine Tumors

N=33

Capecitabin 750 mg/m² x 2 Daily 1-14
Temozolomide 200 mg/m² x 1 10-14

PR 70% (RECIST)
PFS 18 mo

Adverse events (Grade 3/4) 12%

# Temozolomide-Based Chemotherapy in Progressing PDECs After First-Line Chemotherapy

N=25 (GI-NETS)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Tem alone</th>
<th>N=5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tem + Cap</td>
<td>N=13</td>
</tr>
<tr>
<td></td>
<td>Tem + Cap + bev</td>
<td>N=7</td>
</tr>
</tbody>
</table>

| Responses | CR n=1  | (4%) (48 mo) |
|           | PR n=7  | (29%) (median 19 mo) |
|           | SP n=9  | (38%) (median 18 mo) |

| Median PFS | 6 mo (95% CI 4-14 mo) |
| Median OS  | 22 mo (95% CI 8-27 mo) |

| Toxicity                | 1 Grade 3  hematol.tox |
|                        | 1 Grade 3  liver tox |
|                        | 1 patient developed diabetes |

Welin S et al. Cancer 2011
FDG PET/CT

January 4, 2006
May 25, 2006
September 9, 2009

Capecitabin + Temozolomide + Bevacizumab
mTOR inhibitors

Octreo0de

Lanreo0de

Pasireo0de

90Y-DOTATOC

177LuDOTATATE

AMG479
MG0646
Cixutumumumab (IMC-A12)

Gefitinib
Erlotinib
Panitumumumab

Vatalanib
Pazopanib
Sunitinib
Sorafenib
Axitininb

Temsirolimus
Everolimus

Novel somatostatin analogs

IGF-1

IGF-1R

EGF-R

VEGF-R

PDGF-R

IGFR inhibitors
EGFR inhibitors

Angiogenesis inhibitors

VEGF

Bevacizumub

Interferon-α

mTOR inhibitors

Survival
Proliferation
Angiogenesis

Nucleus

sstr-1

sstr-2

sstr-3

sstr-4

sstr-5

sstr-1

sstr-2

sstr-3

sstr-4

sstr-5

5OH-TPH-Hydroxylase

CgA

Pavel M, Neuroendocrinology 2012
Biotherapy: Somatostatin Analogues

Somatostatin

Octreotide acetate

Lanreotide
Novel somatostatin analogue - SOM230

SRIF-14

SMS 201-995

SOM230
Novel cyclohexapeptide
### Binding affinity of different somatostatin analogs to the five somatostatin receptors

<table>
<thead>
<tr>
<th>Compound</th>
<th>sst&lt;sub&gt;1&lt;/sub&gt;</th>
<th>sst&lt;sub&gt;2&lt;/sub&gt;</th>
<th>sst&lt;sub&gt;3&lt;/sub&gt;</th>
<th>sst&lt;sub&gt;4&lt;/sub&gt;</th>
<th>sst&lt;sub&gt;5&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somatostatin</td>
<td>0.93±0.12</td>
<td>0.15±0.02</td>
<td>0.56±0.17</td>
<td>1.35±0.4</td>
<td>0.29±0.04</td>
</tr>
<tr>
<td>Octreotide</td>
<td>280±80</td>
<td>0.38±0.08</td>
<td>7.10±1.4</td>
<td>&gt;1000</td>
<td>6.3±1</td>
</tr>
<tr>
<td>Lanreotide</td>
<td>180±20</td>
<td>0.54±0.08</td>
<td>140±9</td>
<td>230±40</td>
<td>17±5</td>
</tr>
<tr>
<td>SOM230</td>
<td>9.3±0.1</td>
<td>1.0±0.1</td>
<td>1.5±0.3</td>
<td>&gt;100</td>
<td>0.16±0.01</td>
</tr>
</tbody>
</table>

Data are mean IC<sub>50</sub> ±SEM values (nmol/l)

<table>
<thead>
<tr>
<th></th>
<th>Sst1</th>
<th>Sst2</th>
<th>Sst3</th>
<th>Sst4</th>
<th>Sst5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fjällskog et al</td>
<td>19/28</td>
<td>24/28</td>
<td>13/28</td>
<td>26/28</td>
<td>16/28</td>
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<tr>
<td>Kulaksiz et al</td>
<td>21/69</td>
<td>54/69</td>
<td>54/69</td>
<td>ND</td>
<td>53/69</td>
</tr>
<tr>
<td>Papotti et al</td>
<td>30/33</td>
<td>37/48</td>
<td>30/48</td>
<td>8/33</td>
<td>29/48</td>
</tr>
<tr>
<td>Technique</td>
<td>PCR</td>
<td>PCR</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Somatostatin Analogues: Syndrome Control

## Antiproliferative effect of somatostatin analogs in patients with progressive disease

<table>
<thead>
<tr>
<th>SSA</th>
<th>Dosage</th>
<th>n</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lanreotide</td>
<td>3000 µg/day</td>
<td>22</td>
<td>0</td>
<td>1</td>
<td>7</td>
<td>14</td>
<td>Faiss S, J Clin Oncol 2003; 21: 2689-2696</td>
</tr>
<tr>
<td>Lanreotide</td>
<td>30 mg/2 weeks</td>
<td>35</td>
<td>0</td>
<td>1</td>
<td>20</td>
<td>14</td>
<td>Aparicio T, Eur J Cancer 2001; 37: 1014-1019.</td>
</tr>
<tr>
<td>Octreotide</td>
<td>600-1500 µg/day</td>
<td>52</td>
<td>0</td>
<td>0</td>
<td>19</td>
<td>33</td>
<td>Arnold R. Gut 1996; 38: 430-438.</td>
</tr>
<tr>
<td>Octreotide</td>
<td>1500-3000 µg/day</td>
<td>58</td>
<td>0</td>
<td>2</td>
<td>27</td>
<td>29</td>
<td>di Bartolomeo M. Cancer 1996; 77: 402-408.</td>
</tr>
<tr>
<td>Octreotide</td>
<td>600 µg/day</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>5</td>
<td>Arnold R. Digestion 1993; 54 Suppl 1: 72-75</td>
</tr>
<tr>
<td>Lanreotide</td>
<td>15000 µg/day</td>
<td>24</td>
<td>1</td>
<td>1</td>
<td>11</td>
<td>11</td>
<td>Faiss S, J Clin Oncol 2003; 21: 2689-2696</td>
</tr>
<tr>
<td>Lanreotide</td>
<td>30 mg/14 day</td>
<td>31</td>
<td>--</td>
<td>2(7%)</td>
<td>25(81%)</td>
<td>4(13%)</td>
<td>Wymenga AN. J Clin Oncol 1999; 17: 1111.</td>
</tr>
<tr>
<td>Lanreotide</td>
<td>750-12000 µg/day</td>
<td>19</td>
<td>--</td>
<td>1(5%)</td>
<td>12(63%)</td>
<td>6(32%)</td>
<td>Eriksson B. Ann Oncol 1997; 8: 1041-1044.</td>
</tr>
<tr>
<td>Octreotide</td>
<td>20 mg/28 days</td>
<td>15</td>
<td>--</td>
<td>1(7%)</td>
<td>6(40%)</td>
<td>8(53%)</td>
<td>Ricci S. Am J Clin Oncol 2000; 23: 412-415.</td>
</tr>
</tbody>
</table>

|          | **Total**          |     | **1(0,5%)** | **9(4%)** | **132(50%)** | **124(46%)** |

CR: complete remission. PR: partial remission. SD: stable disease. PD: progressive disease
PROMID Study Design

- **Primary endpoint:** time to tumor progression

- Treatment was continued until CT or MRI documented tumor progression (WHO)

- Follow-up until death

- CT and/or MRI were evaluated by a blinded central reader
<table>
<thead>
<tr>
<th></th>
<th>Octreotide LAR (n = 42)</th>
<th>Placebo (n = 43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>63.5 (38-79)</td>
<td>61.0 (39-82)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>male (%)</td>
<td>47.6</td>
<td>53.5</td>
</tr>
<tr>
<td>female (%)</td>
<td>52.4</td>
<td>46.5</td>
</tr>
<tr>
<td>Time since diagnosis, months (range)</td>
<td>7.5 (0.8-271.2)</td>
<td>3.3 (0.8-109.4)</td>
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<tr>
<td>Karnofsky score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤80 (%)</td>
<td>16.7</td>
<td>11.6</td>
</tr>
<tr>
<td>&gt;80 (%)</td>
<td>83.3</td>
<td>88.4</td>
</tr>
<tr>
<td>Carcinoid syndrome* (%)</td>
<td>40.5</td>
<td>37.2</td>
</tr>
<tr>
<td>Resection of primary (%)</td>
<td>69.1</td>
<td>62.8</td>
</tr>
<tr>
<td>Hepatic tumour load</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0%</td>
<td>16.7</td>
<td>11.6</td>
</tr>
<tr>
<td>0%-10%</td>
<td>59.5</td>
<td>62.8</td>
</tr>
<tr>
<td>10%-25%</td>
<td>7.1</td>
<td>4.7</td>
</tr>
<tr>
<td>25%-50%</td>
<td>11.9</td>
<td>9.3</td>
</tr>
<tr>
<td>&gt;50%</td>
<td>4.8</td>
<td>11.6</td>
</tr>
<tr>
<td>Octreoscan positive (%)</td>
<td>76.2</td>
<td>72.1</td>
</tr>
<tr>
<td>Ki-67 up to 2% (%)</td>
<td>97.6</td>
<td>93.0</td>
</tr>
<tr>
<td>CgA elevated (%)</td>
<td>61.9</td>
<td>69.8</td>
</tr>
</tbody>
</table>

* Not requiring octreotide for symptom control

Octreotide LAR 30 mg Significantly Prolongs Time to Tumour Progression

66% reduction in the risk of tumour progression
HR = 0.34; 95% CI: 0.20-0.59; P = .000072

Based on the conservative ITT analysis
TTP = time to progression

TTP Prolonged in Patients Regardless of Carcinoid Syndrome

**Patients without carcinoid syndrome**

- Octreotide LAR: 25 pts / 9 events
- Median TTP 28.8 months
- Placebo: 27 pts / 24 events
- Median TTP 5.91 months

**Patients with carcinoid syndrome**

- Octreotide LAR: 17 pts / 11 events
- Median TTP 14.26 months
- Placebo: 16 pts / 14 events
- Median TTP 5.45 months

HR=0.25 [95% CI: 0.10–0.59]  
\[P=0.0008\]

HR=0.23 [95% CI: 0.09–0.57]  
\[P=0.0007\]

Based on the per protocol analysis

Octreotide LAR 30 mg Provided Improvement in TTP Across Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Time to tumor progression (per protocol analysis)</th>
<th>Hazard Ratio and 95% Confidence Interval for Time to Tumour Progression or Tumour Related Death</th>
</tr>
</thead>
</table>
| Carcinoid syndrome (n=33)                     | Median (months): 14.3 | 5.5 | 0.01  
| Inactive tumour (n=52)                        | Median (months): 28.8 | 5.9 | 0.1  
| Liver involvement 0% (n=12)                   | Median (months): 13.1 | 8.2 | 1    
| Liver involvement 0-10% (n=52)                | Median (months): 29.4 | 6.1 | 10   
| Liver involvement 10-50% (n=14)               | Median (months): 11.2 | 5.5 | 10   
| Liver involvement >50% (n=7)                  | Median (months): 4.6  | 2.8 | 10   
| Chromogranin A elevated (n=56)                | Median (months): 14.3 | 5.6 | 0.01  
| Chromogranin A not elevated (n=27)            | Median (months): 28.8 | 8.5 | 0.1  
| Karnofsky Index >80% (n=73)                   | Median (months): 27.1 | 5.8 | 1    
| Karnofsky Index ≤80% (n=12)                   | Median (months): 11.5 | 6.1 | 10   
| Age <63 years (n=43)                          | Median (months): 28.8 | 8.3 | 1    
| Age ≥63 years (n=42)                          | Median (months): 14.3 | 5.7 | 10   
| Primary tumour resected (n=56)                | Median (months): 29.4 | 5.9 | 0.01  
| Primary tumour not resected (n=29)            | Median (months): 10.3 | 5.6 | 0.1  

Arnold R. Presented at ASCO-GI 2009
• Most favorable treatment outcome in patients with
  – Hepatic tumor load <10% ($P<0.0009$)
  – Resected primary ($P<0.0104$)
• Benefit of octreotide LAR versus placebo seen irrespective of
  – Functioning or nonfunctioning NETs
  – Elevated or non-elevated CgA
Study aim and design

**CLARINET**  
(Controlled study of Lanreotide Antiproliferative Response In NET)

**Aim**
- To compare effect of lanreotide Autogel 120 mg vs. placebo on PFS in well-/moderately differentiated non-functioning GEP-NETs

**Design**
- International multicentre randomized double-blind placebo-controlled phase 3 study

![Study visit timeline](chart)

1. **ClinicalTrials.gov** NCT00353496; EudraCT 2005-004904-35.
Patient population

- Sporadic non-functioning GEP-NET*
- Well-/moderately-differentiated tumour with low proliferation index (Ki-67 <10%)
- Metastatic and/or locally advanced inoperable tumour
- Tumour measurable according to RECIST criteria v1.0 (central assessment)
- Grade ≥2 on somatostatin receptor scintigraphy (Krenning scale)
- No use of interferon, chemoembolization or chemotherapy in previous 6 months, and SSA naive

* Including gastrinomas with adequate symptom control with PPIs and NETs of unknown primary origin.
Patient disposition

204 patients randomized

101 received lanreotide Autogel 120 mg
- Events*: 30 PD, 2 deaths
  - 18 withdrawals
    - 6 due to investigator decision (PD)
    - 3 due to AEs
    - 3 withdrew consent
    - 2 protocol violations
    - 4 other reasons
- 53 completed the study without events

103 received placebo
- Events*: 58 PD, 2 deaths
  - 21 withdrawals
    - 9 due to investigator decision (PD)
    - 3 due to AEs
    - 5 withdrew consent
    - 2 protocol violations
    - 2 other reasons
- 26 completed the study without events

*2 deaths occurred in lanreotide group after withdrawal for another reason; and 2 deaths occurred and 2 PDs detected in placebo group after withdrawal for another reason.
## Baseline characteristics (ITT population, N=204)

<table>
<thead>
<tr>
<th></th>
<th>Lanreotide Autogel (n=101)</th>
<th>Placebo (n=103)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>53 (52)</td>
<td>54 (52)</td>
</tr>
<tr>
<td><strong>Age in years, mean (SD)</strong></td>
<td>63 (10)</td>
<td>62 (11)</td>
</tr>
<tr>
<td><strong>Time since diagnosis in months, mean (SD)</strong></td>
<td>33 (46)</td>
<td>34 (41)</td>
</tr>
<tr>
<td><strong>Primary tumour resected, n (%)</strong></td>
<td>40 (40)</td>
<td>39 (38)</td>
</tr>
<tr>
<td><strong>NET origin, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreas</td>
<td>42 (42)</td>
<td>49 (48)</td>
</tr>
<tr>
<td>Midgut</td>
<td>33 (33)</td>
<td>40 (39)</td>
</tr>
<tr>
<td>Hindgut</td>
<td>11 (11)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Unknown/Other</td>
<td>15 (15)</td>
<td>11 (11)</td>
</tr>
<tr>
<td><strong>Chromogranin A, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤1 × ULN</td>
<td>33 (33)</td>
<td>34 (33)</td>
</tr>
<tr>
<td>1–2 × ULN</td>
<td>25 (25)</td>
<td>18 (17)</td>
</tr>
<tr>
<td>&gt;2 × ULN</td>
<td>41 (41)</td>
<td>48 (47)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (2)</td>
<td>3 (3)</td>
</tr>
</tbody>
</table>
Primary endpoint: PFS (primary ITT analysis)

- PFS substantially prolonged with lanreotide Autogel 120 mg for metastatic well-/moderately differentiated GEP-NETs
  - 53% risk reduction for progression/death

Lanreotide Autogel vs. placebo
P = 0.0002 HR = 0.47 [95% CI: 0.3, 0.7]

- Effects on PFS according to tumour localization, tumour grade & hepatic tumour load will also be presented

P-value derived from stratified logrank test; GEP-NETs, gastroenteropancreatic NETs; HR derived from Cox proportional hazard model. HR, hazard ratio; ITT, intention-to-treat
Subgroup analyses (ITT)
Midgut vs. pancreatic NETs

**Midgut NETs (n=73)**
Lanreotide Autogel vs. placebo
p=0.0091 HR=0.35 [95% CI: 0.16, 0.80]

- **Lanreotide Autogel 120 mg**
  - 8 events / 33 patients
  - median, not reached

- **Placebo**
  - 21 events / 40 patients
  - median, 21.1 months [95% CI: 17.0, NC]

**pNETs (n=91)**
Lanreotide Autogel vs. placebo
p=0.0637 HR=0.58 [95% CI: 0.32, 1.04]

- **Lanreotide Autogel 120 mg**
  - 18 events / 42 patients
  - median, not reached

- **Placebo**
  - 31 events / 49 patients
  - median, 12.1 months [95% CI: 9.4, 18.3]

P-value derived from log-rank test; HR derived from Cox proportional hazards model. NC, not calculable.
Subgroup analyses (ITT)
Effect of hepatic tumour load

**Tumour load ≤25% (n=137)**
Lanreotide Autogel vs. placebo
p=0.0002 HR=0.34 [95% CI: 0.18, 0.62]

**Tumour load >25% (n=67)**
Lanreotide Autogel vs. placebo
p=0.0170 HR=0.45 [95% CI: 0.23, 0.88]

- **Lanreotide Autogel 120 mg**
  - 14 events / 62 patients
  - median, not reached

- **Placebo**
  - 41 events / 75 patients
  - median, 21.1 months [95% CI: 17.6, 24.4]

- **Lanreotide Autogel 120 mg**
  - 18 events / 39 patients
  - median, 24.1 months [95% CI: 9.3, NC]

- **Placebo**
  - 19 events / 28 patients
  - median, 9.4 months [95% CI: 6.3, 12.0]

P-value derived from log-rank test; HR derived from Cox proportional hazards model. NC, not calculable.
Overall survival (ITT)

Randomized double-blind study for ≤96 weeks*

Post study survival phase*

Lanreotide Autogel 120 mg vs. placebo p=0.8791

Lanreotide
19 deaths / 101 patients

Placebo
17 deaths / 103 patients

P-value derived from log-rank test.
* Survival was followed throughout the randomized study for patients on study medication for up to 96 weeks or until early withdrawal / PD, and then continued to be followed during the post-study survival phase (when the patient may or may not have continued or switched to lanreotide).
# Tolerability of Somatostatin Analogues

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steatorrhoea</td>
<td>39.3%</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>37.3%</td>
</tr>
<tr>
<td>Flatulence</td>
<td>28.1%</td>
</tr>
<tr>
<td>Pain at injection site</td>
<td>28.1%</td>
</tr>
<tr>
<td>Gall stones</td>
<td>17.9%</td>
</tr>
<tr>
<td>Emesis</td>
<td>11.5%</td>
</tr>
<tr>
<td>Hyperglycaemia</td>
<td>10.8%</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>4.3%</td>
</tr>
<tr>
<td>Cholangitis</td>
<td>4.3%</td>
</tr>
<tr>
<td>Septicaemia</td>
<td>&lt; 1%</td>
</tr>
</tbody>
</table>

- Most side effects are transient
- More than 25 years of experience
- Very good long-term tolerability


• Cyclohexapeptide engineered to bind to multiple somatostatin receptor subtypes (i.e. 1, 2, 3, and 5)

• In pre-clinical models, pasireotide exhibits anti-angiogenic activity by inhibiting VEGF secretion and reduces the incidence and size of pituitary tumours
Differential binding affinities of somatostatin, octreotide and pasireotide
Pasireotide sc: Phase II Study in Patients with Carcinoid Syndrome

45 Patients refractory to Octreotide: ≥ 4 Stools or ≥ 2 Flushings/day

Patients with carcinoid syndrome refractory or resistant to octreotide LAR

Initial dose pasireotide sc 300 µg /bid with dose increase as needed every 3 days for symptom control up to maximum 900 µg/bid

Response in Patients treated with Pasireotide

12/44 patients (27%): symptomatic improvement

**Side effects:** Nausea 27%, abdominal pain 31%, weight loss 22%, fatigue 22%

BM = Bowel movements

Kvols L et al., auf ASCO-GI 2006
Primary endpoint:
• Reduction in bowel movements and/or flushing episodes at 24 weeks

Secondary endpoints:
• Objective tumour response
• Disease control rate
• Quality of Life
• Biochemical markers

ClinicalTrials.gov Identifier:NCT00690430
Study Design
Best Percentage Tumor Shrinkage From Baseline

- Pastreotide LAR (n = 42)
- Octreotide LAR (n = 50)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Pastreotide LAR</th>
<th>Octreotide LAR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zero change in best percentage change from baseline</td>
<td>4 (9.5%)</td>
<td>5 (10.0%)</td>
</tr>
<tr>
<td>Decrease in best percentage change from baseline</td>
<td>21 (50.0%)</td>
<td>19 (38.0%)</td>
</tr>
<tr>
<td>Increase in best percentage change from baseline</td>
<td>15 (35.7%)</td>
<td>20 (40.0%)</td>
</tr>
<tr>
<td><strong>% change in target lesion available but contradicted by overall lesion response = PD</strong></td>
<td>2 (4.8%)</td>
<td>6 (12.0%)</td>
</tr>
</tbody>
</table>
Kaplan-Meier Plot of Investigator-Assessed Progression-Free Survival
Antiproliferative Effect of Somatostatin Analogs

Binding of the somatostatin receptor on tumor cells

Systemic activity

DIRECT ANTIPROLIFERATIVE EFFECT

- Inhibition of cell cycle
- Inhibition of growth factor effects
- Pro-apoptotic effect

INDIRECT ANTIPROLIFERATIVE EFFECT

- Inhibition of the release of growth factor and trophic hormones
- Inhibition of cell angiogenesis
- Modulation of immune system

Adapted from Susini & Buscail Ann. Oncol. 2006
TIME INTERFERON
The IF Drug For Cancer
EFFECTS OF LEUKOCYTE INTERFERON ON CLINICAL SYMPTOMS AND HORMONE LEVELS IN PATIENTS WITH MID-GUT CARCINOID TUMORS AND CARCINOID SYNDROME

K. Öberg, M.D., K. Funa, M.D., and G. Alm, M.D.

Abstract We treated nine patients who had carcinoid tumors of the small intestine, six of whom had the carcinoid syndrome, with daily intramuscular doses of leukocyte interferon — $3 \times 10^6$ U per day for one month and $6 \times 10^6$ U per day for another two months. Seven patients had previously been treated with streptozocin and fluorouracil, without benefit.

Treatment with interferon ameliorated the manifestations of the carcinoid syndrome and led to prompt and continuing decreases in urinary levels of 5-hydroxyindoleacetic acid and serum levels of human choriomic gonadotropin subunits and pancreatic polypeptide in all six patients with liver metastases, but it had no clear effect in two of three patients with only lymph-node involvement. After the treatment period, five of the six responders had relapses in clinical manifestations and increases in hormone levels.

We conclude that interferon is of benefit in treating metastatic small intestinal carcinoid tumors in patients with the carcinoid syndrome. (N Engl J Med 1983; 309:129-33.)
Interferon- Mechanisms of action

Direct and indirect effects
- Inhibition of secretion
- Inhibition of proliferation (cell cycle arrest G1-S phase)
- Induction of apoptosis
- Antiangiogenic effects
- Immunomodulation (NKC, Macrophages)

Interferon receptor coupled
Activation of JAK–STAT pathways

Induction of Interferon inducible genes
p21, p27, 2-5-A-Synthetase, IFR-1, IRF-2)

Platanias et al Nature Reviews Immunology 5, 2005
Interferon Preparations and Doses

- Individually titrated in each patient
- Leucocyte count lower normal level (~3x10⁹/L)
  - α-Interferon 1½-3-5 MU 3-5 times per week
- Pegylated α-Interferon 75-150 µg per week
- Use acetaminophen for flu-like side effects
Interferon NET studies

- 27 studies, 679 patients
- Interferon doses: $16 \pm 11$ MU/w (3-5 MU 3x/week)
- Study period $39 \pm 35$ weeks (2-170 weeks)
- Symptomatic response 62\% (29-100\%)
- Biochemical response 50\% (9-100\%)
- Tumor response
  - Regression 10\% (0-25\%)
  - Stabilization 65\% (38-94\%)
  - Progression 23\% (6-50\%)
Pegylated IFN-α in patients with NET

**Mixture of NETs**  
*n=17*

- **PEG-IFN-α 2b**  
  - 50-100 µg/W

- **Tumor response**  
  - PR 2/17
  - SD 11/17

- **Median duration (PFS)**  
  - 13 mo

- **Biochemical response**  
  - PR 6/13
  - SD 6/13

**Adverse effects**

- No WHO-grade 3-4
- Fatigue, flu-like symptom (47/24%)
- Elevation of liver transaminases 41%
# Interferon Alpha in the Management of NET; A Retrospective Study in 37 Patients

<table>
<thead>
<tr>
<th>N=37</th>
<th>21 midgut</th>
<th>G1 49%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>7 pancreatic</td>
<td>G2 41%</td>
</tr>
<tr>
<td></td>
<td>6 unknown</td>
<td>G3 5%</td>
</tr>
<tr>
<td></td>
<td>3 miscellaneous</td>
<td></td>
</tr>
</tbody>
</table>

**Treatment**

- IFN-α, 3MU x 3/w
- + SMS 76%
- CR 3%
- PR 3%
- SD 70%
- PD 24%

**Median TTP** 14 Mo

**Adverse events** 30% (Flu-like symptoms, fatigue, hypothyroidism)

*Mirvis et al. ENETS Conference Barcelona, 2013*
Multiple Cellular Effects of α-IFN

Binding of the interferon receptor

**Direct effects**
- Cell cycle inhibition G1/S
- Induction of bcl-2
- Inhibition of growth factor/receptor expression
- Upregulation of SSTR-2

**Indirect effects**
- Stimulation of the immune system
  - Cytotoxic T-cells
  - NK-cells
  - Monocytes/Macrophages
- Stimulation of other cytokines
- Anti-angiogenesis
Interferon and somatostatin receptors
Interferon and somatostatin analogues

- 3 randomised trials INF and SS-analogues
  - Octreotide vs. INF + Octreotide (68 + 105 pt.)
  - INF vs. Lanreotide vs. INF + Lanreotide (80 pt.)

Faiss J Clin Oncol 2003,
Kölby Br J Surg 2003,
Arnold Clin Gastroenterol Hepatol 2005

- Is combination therapy better than either treatment alone?
<table>
<thead>
<tr>
<th>Group</th>
<th>5 year survival rate</th>
<th>Risk of tumour progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>I: Sandostatin (n=33)</td>
<td>36.6%</td>
<td>p=0.132</td>
</tr>
<tr>
<td>II: Sandostatin + IFN-alpha (n=33)</td>
<td>56.8%</td>
<td>p=0.008</td>
</tr>
</tbody>
</table>

All midgut carcinoids
Pasireotide + IFN-α

Patient UBL - Chromogranin A

CgA µg/ml

Months

SOM 230
SOM230+α-IFN
NET and angiogenesis
## Antiangiogenic drugs: results from novel combinations

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Targets</th>
<th>N</th>
<th>Primary tumor sites</th>
<th>PD at study entry</th>
<th>Objective Response: PR (%) ; SD (%)</th>
<th>PFS/ TTP (months)</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vatalanib (PTK/ZK)</td>
<td>VEGFR-1,2,3 (PDGFR, c-kit)</td>
<td>17</td>
<td>Mixed NET</td>
<td>Yes</td>
<td>0% PR 50% SD</td>
<td>7.0 (3-23)</td>
<td>35%: G3-4</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>C-RAF, B-RAF VEGFR-2, -3, PDGFR-ß, KIT</td>
<td>42</td>
<td>Carcinoid pNET</td>
<td>No</td>
<td>9% PR 10% MR SD not rep.</td>
<td>n.d.</td>
<td>43%: G3-4 (skin, GI, fatigue)</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>VEGFR, PDGFR, c-kit</td>
<td>41</td>
<td>Carcinoid pNET</td>
<td>No</td>
<td>11% PR 83% SD</td>
<td>10*</td>
<td>25%: G3-4</td>
</tr>
<tr>
<td>vs Placebo</td>
<td>VEGFR, PDGFR, c-kit</td>
<td>86</td>
<td>pNET</td>
<td>Yes</td>
<td>2.3% CR 7% PR 62.8% SD 0% PR; 60% SD</td>
<td>11.4</td>
<td>10-12%: G3-4 Neutropenia Hypertension</td>
</tr>
<tr>
<td>Pazopanib + Octreotide</td>
<td>VEGFR-1, -2, and -3, PDGFR-ß, c-kit</td>
<td>31</td>
<td>pNET Carcinoid</td>
<td></td>
<td>12% PR∞ 69% SD</td>
<td>12.7*</td>
<td>12%: G3/4 Hypertension</td>
</tr>
<tr>
<td>Bevacizumab + Octreotide; (+ PEG-IFN at wk 16)</td>
<td>VEGF SSTR</td>
<td>22</td>
<td>Advanced carcinoid: Mixed NET</td>
<td>No</td>
<td>18% PR 77% SD</td>
<td>15.7*</td>
<td>5%: G3-4 36% (HTN)</td>
</tr>
<tr>
<td>Bevacizumab + Sorafenib</td>
<td>VEGF; C-RAF, B-RAF VEGFR-2, -3, PDGFR-ß, KIT</td>
<td>31</td>
<td>Carcinoid pNET</td>
<td></td>
<td>9.8% PR 95% DCR</td>
<td>12.4</td>
<td>20%: G3/4 hand-foot syndrome; 16% asthenia</td>
</tr>
<tr>
<td>Bevacizumab + Temozolomide</td>
<td>VEGF MGMT</td>
<td>29</td>
<td>pNET Carcinoid</td>
<td></td>
<td>24% PR/ 70%SD 0% PR / 9% SD</td>
<td>62%: G3/4</td>
<td></td>
</tr>
<tr>
<td>Bevacizumab + Oxaliplatin + Capecitabine</td>
<td>VEGF</td>
<td>40</td>
<td>Mixed NET</td>
<td>40%</td>
<td>18% PR∞ 63% SD</td>
<td>14.1</td>
<td></td>
</tr>
</tbody>
</table>

**SWOG 0518: Bevacizumab + octreotide vs Interferon + octreotide**

**Phase III Open Labeled—Ongoing**

**Advanced Carcinoid with poor prognosis**
- PD
- Refractory syndrome
- G2 with 6+ lesion

(N=400)

**Randomization:** 1:1

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

- **Interferon 5 mu 3 d/wk**
  - octreotide LAR 20 mg q21 d

**Treatment until disease progression**

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

**Primary end point:**
- PFS (RECIST)

**Secondary end points:**
- Tumor response, OS, biomarkers, safety
(More than) Angiogenesis inhibitors

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>PDGFR</th>
<th>VEGFR</th>
<th>FGFR</th>
<th>FLT3</th>
<th>EGFR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sunitinib</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Pazopanib</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AMG706</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Dovitinib</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>
Sunitinib vs Placebo in Advanced pNET

- Phase III randomised, placebo-controlled, double-blind trial
- Trial terminated after unplanned early analysis

Well differentiated advanced pNET patients
(N = 171 enrolled / 340 planned)
- Disease progression in past 12 months
- Not amenable to curative treatment

**Primary Endpoint:**
PFS
Statistical significance required nominal critical $z$ value $\geq 3.8809$

**Secondary Endpoints:**
OS
ORR
TTR
Duration of response
Safety
Patient-reported outcomes

Sunitinib 37.5 mg/day orally
Continuous daily dosing*
$n = 86$

Placebo*
$n = 85$

* With best supportive care
Somatostatin analogues were permitted

## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Sunitinib (n = 86)</th>
<th>Placebo (n = 85)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age, yr (range)</strong></td>
<td>56 (25–84)</td>
<td>57 (26–78)</td>
</tr>
<tr>
<td><strong>Male, n</strong></td>
<td>42</td>
<td>40</td>
</tr>
<tr>
<td><strong>Female, n</strong></td>
<td>44</td>
<td>45</td>
</tr>
<tr>
<td><strong>ECOG Performance Status, n</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0/1/2</td>
<td>53/33/0</td>
<td>41/43/1</td>
</tr>
<tr>
<td><strong>Number of disease sites, n</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/ 2/ ≥3</td>
<td>30/31/24</td>
<td>23/26/35</td>
</tr>
<tr>
<td><strong>Presence of distant metastases, n</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any, including hepatic</td>
<td>82</td>
<td>80</td>
</tr>
<tr>
<td>Extrahepatic</td>
<td>21</td>
<td>34</td>
</tr>
<tr>
<td><strong>Prior Therapies, n</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somatostatin analogues</td>
<td>30</td>
<td>32</td>
</tr>
<tr>
<td>Systemic chemotherapy</td>
<td>57</td>
<td>61</td>
</tr>
<tr>
<td>Streptozocin</td>
<td>24</td>
<td>28</td>
</tr>
<tr>
<td>Anthracyclines</td>
<td>27</td>
<td>35</td>
</tr>
<tr>
<td>Fluoropyrimidines</td>
<td>20</td>
<td>25</td>
</tr>
</tbody>
</table>

Sunitinib Phase III Trial: PFS by Investigator Review

- **Sunitinib (n = 86)**
  - Median, 11.4 months
- **Placebo (n = 85)**
  - Median, 5.5 months

**HR, 0.418**

**95% CI, 0.263-0.662**

**P = 0.000118*\)**

*P-value might be misleading due to multiple early looks

- **P-value did not cross adjusted efficacy boundary when accounting for early data looks by IDMC**
- **PFS at 6 months:** 71.3% for sunitinib; 43.2% for placebo
  - Further PFS analyses not performed due to early termination of study
- **Hazard ratio is obtained from Cox proportional hazards model**

Sunitinib Phase III Trial: Summary of PFS Analyses

<table>
<thead>
<tr>
<th>PFS Analysis</th>
<th>Events n</th>
<th>Events Censored n</th>
<th>Median Difference in PFS months</th>
<th>HR</th>
<th>P Value Cross-Efficacy Boundary?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigator</td>
<td>81</td>
<td>90</td>
<td>5.9</td>
<td>0.42</td>
<td>No</td>
</tr>
<tr>
<td>Central radiology</td>
<td>61</td>
<td>110</td>
<td>6.8</td>
<td>0.32</td>
<td>N/A</td>
</tr>
<tr>
<td>FDA*</td>
<td>82</td>
<td>89</td>
<td>4.8</td>
<td>0.43</td>
<td>No</td>
</tr>
</tbody>
</table>

*When accounting for early data looks by DMC.

2 The FDA did an additional analysis and found a median PFS of 10.2 months for sunitinib and 5.4 months for placebo. These data were used in the Sutent prescribing information.

Sunitinib Phase III Trial: PFS by Investigator Subgroup Analysis

![Graph showing HR and 95% CI for various patient subgroups.]

- **All Patients**: 171
  - **HR**: 0.418
  - **95% CI**: (0.263, 0.662)

- **Age <65 years**: 126
  - **HR**: 0.474
  - **95% CI**: (0.284, 0.793)

- **Age ≥65 years**: 45
  - **HR**: 0.223
  - **95% CI**: (0.071, 0.702)

- **White**: 101
  - **HR**: 0.487
  - **95% CI**: (0.257, 0.923)

- **Non-White**: 70
  - **HR**: 0.353
  - **95% CI**: (0.179, 0.695)

- **Male**: 82
  - **HR**: 0.374
  - **95% CI**: (0.200, 0.701)

- **Female**: 89
  - **HR**: 0.477
  - **95% CI**: (0.242, 0.939)

- **ECOG PS 0**: 94
  - **HR**: 0.404
  - **95% CI**: (0.222, 0.735)

- **ECOG PS 1/2**: 77
  - **HR**: 0.455
  - **95% CI**: (0.219, 0.943)

- **≤2 disease sites**: 112
  - **HR**: 0.435
  - **95% CI**: (0.245, 0.772)

- **≥3 disease sites**: 59
  - **HR**: 0.428
  - **95% CI**: (0.195, 0.941)

- **Extrahepatic distant disease**: 55
  - **HR**: 0.536
  - **95% CI**: (0.245, 1.170)

- **Pancreas/liver only disease**: 114
  - **HR**: 0.414
  - **95% CI**: (0.233, 0.736)

- **No somatostatin analogs used**: 103
  - **HR**: 0.409
  - **95% CI**: (0.222, 0.752)

- **Somatostatin analogs used***: 68
  - **HR**: 0.428
  - **95% CI**: (0.206, 0.887)

- **0 or 1 previous systemic regimens**: 121
  - **HR**: 0.334
  - **95% CI**: (0.188, 0.594)

- **≥2 previous systemic regimens**: 50
  - **HR**: 0.607
  - **95% CI**: (0.269, 1.370)

- **Non-functioning tumour**: 86
  - **HR**: 0.264
  - **95% CI**: (0.129, 0.539)

- **Functioning tumour**: 46
  - **HR**: 0.747
  - **95% CI**: (0.303, 1.841)

- **Ki-67 ≤5%**: 43
  - **HR**: 0.378
  - **95% CI**: (0.155, 0.922)

- **Ki-67 >5%**: 29
  - **HR**: 0.634
  - **95% CI**: (0.235, 1.711)

- **Time from diagnosis <3 years**: 89
  - **HR**: 0.433
  - **95% CI**: (0.239, 0.786)

- **Time from diagnosis ≥3 years**: 82
  - **HR**: 0.292
  - **95% CI**: (0.130, 0.657)

---

*Includes all patients receiving somatostatin analogs at any time before and/or concomitant with study treatment.

ECOG PS, Eastern Cooperative Oncology Group Performance Score; HR, hazard ratio.

Kaplan Meier estimates of OS

Hazard ratio: 0.737
95% CI: 0.465-1.168
P = 0.1926

Sunitinib (N=86, death=34))
Median: 30.5 months

Placebo (N=85, death=39))
Median: 24.4 months

Number of subjects at risk
Sunitinib 86 83 77 73 69 59 49 41 31 18 10 5 1
Placebo 85 75 68 61 55 49 39 32 24 18 11 4

Sunitinib: Treatment-Related Adverse Events >20%

<table>
<thead>
<tr>
<th>Treatment duration: median (range)</th>
<th>Sunitinib (n=83)</th>
<th>Placebo (n=82)</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>no of patients (%)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>49 (59)</td>
<td>4 (5)</td>
</tr>
<tr>
<td>Nausea</td>
<td>37 (45)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>28 (34)</td>
<td>4 (5)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>28 (34)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>27 (32)</td>
<td>4 (5)</td>
</tr>
<tr>
<td>Hair-colour changes</td>
<td>24 (29)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>24 (29)</td>
<td>10 (12)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>23 (28)</td>
<td>4 (5)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>22 (26)</td>
<td>8 (10)</td>
</tr>
<tr>
<td>Palmar-plantar erythrodysesthesia</td>
<td>19 (23)</td>
<td>5 (6)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>18 (22)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>18 (22)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>17 (20)</td>
<td>0</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>17 (20)</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

*Cardiac failure leading to death was reported in 2/83 (2%) patients on Sunitinib and no patients on placebo.

Summary Sunitinib

- Sunitinib provided a clinically meaningful 5.9 month improvement in median PFS compared with placebo in patients with advanced pNET in all subgroups.

- Due to the early termination of the study, the FDA performed an additional analysis, and found a mean difference in PFS of 4.8 months\(^2\).

- 6-month survival for patients treated with sunitinib was 92.6%.

- Toxicities were consistent with those observed in other trials of sunitinib.

### Phase II Study of Pazopanib Monotherapy in Metastatic GEP-NETs

| N | pancreatic | 13 |
| 8 colorectal | 8 |
| miscellaneous | 14 |

**Treatment**  
Pazopanib, 800 mg/d

**Results**  
PR 19%  
Disease control CR+PR+SD 76%

*Park, YS, et al. ENETS Conference Barcelona, 2013*
The mTOR pathway

- Signaling to mTOR from growth factors and nutrients is mediated through PI3K, Akt and the TSC proteins TSC1 and TSC2.

- mTOR acts as a sensor of available nutrients & consolidates this information with signaling from growth factors.

- mTOR directs the translation of numerous regulatory proteins involved in:
  - cell growth and proliferation,
  - cellular metabolism
  - angiogenesis

- Targets of mTOR are 4-EBP-1 and S6 Kinase 1
  - (ribosomal translation of mRNA into protein)

- TSC proteins function as a heterodimer to inhibit mTOR activity through Rheb

mTOR exists in two multiprotein complexes, mTOR complexes 1 and 2 (mTORC1 and mTORC2)

4E-BP1 eukaryotic translation initiation factor 4E (eIF-4E) binding protein-1
S6 kinase 1 (S6K1)

JAK/STAT pathway in MPNs. Upon cytokine binding, JAK2 molecules are recruited and activated by cytokine receptors, which results in phosphorylation of downstream signaling pathways such as phosphoinositide 3-kinase (PI3K), RAS, and STAT3/5.


©2013 by American Association for Cancer Research
mTOR Pathway and Sporadic pNETs

The RADIANT Study Programme
*(RAD001 In Advanced Neuroendocrine Tumors)*

<table>
<thead>
<tr>
<th>Study</th>
<th>Phase</th>
<th>Patients</th>
<th>Treatment Arms</th>
<th>Primary Endpoints</th>
<th>Secondary Endpoints</th>
</tr>
</thead>
</table>
| RADIANT-1 | II    | Patients with advanced pNETs progressing during or after chemotherapy  
*N=160*            | Everolimus; Everolimus + Octreotide LAR (2 Strata)            | Objective Response Rate with Everolimus monotherapy (Stratum 1) | Objective Response Rate with combination therapy (Stratum 2), PFS, Response duration, OS and safety and pharmacokinetics in both strata |
| RADIANT-2 | III   | Patients with advanced NET and a history of secretory symptoms  
*N = 429*          | Everolimus + Octreotide LAR vs. Placebo + Octreotide LAR  | PFS  
*Statistical boundary: \*p \*≤ .0246*              | OS ORR Biomarkers Safety PK                                                                 |
| RADIANT-3 | III   | Patients with progressive advanced  
*pNET*  
*N=410*                | Everolimus + best supportive care vs. Placebo + best supportive care | PFS  
*Statistical boundary ≤ .025*                    | OS ORR Biomarkers Safety PK                                                                 |
RADIANT-1: Study Design

Advanced pancreatic NET with RECIST progression following cytotoxic chemotherapy

- **Stratum 1**: No octreotide LAR 60 days prior to enrollment; received everolimus 10 mg/d
- **Stratum 2**: Octreotide LAR ≥3 months prior to enrollment; received everolimus 10 mg/d + octreotide LAR (≤30 mg, q28d)

Stratum 1
115 patients

**Everolimus**

Stratum 2
45 patients

**Everolimus and octreotide LAR**

Treatment continues until tumor progression

Multiphasic CT or MRI performed at baseline and every 3 mo

**Primary end point**
- RR stratum 1

**Secondary end point**
- RR stratum 2
- Response duration
- Safety
- PFS
- Survival
- PK
**RADIANT-1: Best Percentage Change Central Radiology Review**

**Stratum 1: Everolimus**

(n = 115)

<table>
<thead>
<tr>
<th></th>
<th>Central radiology</th>
<th>ITT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial response</td>
<td>11 (9.6)</td>
<td></td>
</tr>
<tr>
<td>Stable disease</td>
<td>78 (67.8)</td>
<td></td>
</tr>
<tr>
<td>Clinical benefit (PR + SD)</td>
<td>89 (77.4)</td>
<td></td>
</tr>
<tr>
<td>Progressive disease</td>
<td>16 (13.9)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>10 (8.7)</td>
<td></td>
</tr>
</tbody>
</table>

**Stratum 2: Everolimus + Octreotide LAR**

(n = 45)

<table>
<thead>
<tr>
<th></th>
<th>Central radiology</th>
<th>ITT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial response</td>
<td>2 (4.4)</td>
<td></td>
</tr>
<tr>
<td>Stable disease</td>
<td>36 (80.0)</td>
<td></td>
</tr>
<tr>
<td>Clinical benefit (PR + SD)</td>
<td>38 (84.4)</td>
<td></td>
</tr>
<tr>
<td>Progressive disease</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>7 (15.6)</td>
<td></td>
</tr>
</tbody>
</table>

*Results contradicted by overall lesion response or †unknown.

RADIANT-1 PFS by Central Review

Everolimus

N = 115
Median PFS = 9.7 mo

Patients at risk:
115 111 81 58 54 36 25 15 12 5 3 3 1 0

Everolimus + Octreotide LAR

N = 45
Median PFS = 16.7 mo

Patients at risk:
45 39 32 22 21 19 14 10 8 3 3 1 0

### Glycemic Control in Insulinoma Treated With Everolimus

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age/Gender</th>
<th>Institution</th>
<th>Glucose control at study entry</th>
<th>Glucose control during everolimus</th>
<th>Tumor response PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>57/female</td>
<td>MDACC</td>
<td>Depot octreotide, diazoxide, dexamethasone, and continuous enteral feeding</td>
<td><strong>Normalization of glucose</strong>; discontinuation of diazoxide and nocturnal feedings</td>
<td>Partial response 16 mo</td>
</tr>
<tr>
<td>Patient 2</td>
<td>40/female</td>
<td>MDACC</td>
<td>Depot octreotide, diazoxide, and glucose tablets</td>
<td><strong>Normalization of glucose</strong>; discontinuation of diazoxide and glucose tablets</td>
<td>Partial response 29 mo</td>
</tr>
<tr>
<td>Patient 3</td>
<td>22/female</td>
<td>DFCI</td>
<td>Intermittent symptomatic hypoglycemia despite use of depot octreotide and diazoxide</td>
<td><strong>Normalization of glucose</strong> and discontinuation of diazoxide</td>
<td>Stable disease 6+ mo</td>
</tr>
<tr>
<td>Patient 4</td>
<td>66/male</td>
<td>UCSF</td>
<td>Glucose control requiring nocturnal dextrose infusion</td>
<td><strong>Normalization of glucose</strong> and discontinuation of nocturnal dextrose infusions</td>
<td>Stable disease 6+ mo</td>
</tr>
</tbody>
</table>

Inhibition of mTOR Reduces Insulin Gene Transcription and DNA Synthesis

Insulin-producing cell

- Insulin receptor
- ↓ Glucose
- ↓ Nutrient

- LKB1
- AMPK
- TSC 1/2
- Akt
- mTOR
- Insulin production
- Insulin release
- Growth

Peripheral tissue

- Insulin receptor
- PI3-K
- PDK
- Akt
- mTOR
- RAD001
- Glucose transport
- Nutrient metabolism

- PTEN

Regulatory pathway:
- RAD001
Everolimus for Advanced Pancreatic Neuroendocrine Tumors

James C. Yao, M.D., Manisha H. Shah, M.D., Tetsuhide Ito, M.D., Ph.D.,
Catherine Lombard Bohas, M.D., Edward M. Wolin, M.D.,
Eric Van Cutsem, M.D., Ph.D., Timothy J. Hobday, M.D., Takuji Okusaka, M.D.,
Jaume Capdevila, M.D., Elisabeth G.E. de Vries, M.D., Ph.D.,
Paola Tomassetti, M.D., Marianne E. Pavel, M.D., Sakina Hoosen, M.D.,
Tomás Haas, Ph.D., Jeremie Lincy, M.Sc., David Lebwohl, M.D.,
and Kjell Öberg, M.D., Ph.D., for the RAD001 in Advanced Neuroendocrine Tumors, Third Trial (RADIANT-3) Study Group
RADIANT-3 Study Design

Phase III Double-Blind, Placebo-Controlled Trial

Patients with progressive advanced pNET, N=410
- Advanced low- or intermediate-grade pNET
- Radiologic progression ≤12 months
- Prior anti-tumour therapy allowed
- WHO PS ≤2

Stratified by:
- WHO PS
- Prior chemotherapy

Primary Endpoint:
PFS
Statistical boundary ≤.025

Secondary Endpoints:
OS
ORR
Biomarkers
Safety
PK

Randomisation: August 2007-May 2009
* Concurrent somatostatin analogues allowed

## RADIANT-3: Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Everolimus (n = 207)</th>
<th>Placebo (n = 203)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age, years (range)</strong></td>
<td>58 (23-87)</td>
<td>57 (20-82)</td>
</tr>
<tr>
<td><strong>Male : Female (%)</strong></td>
<td>53 : 47</td>
<td>58 : 42</td>
</tr>
<tr>
<td><strong>WHO PS (%)</strong></td>
<td>67 / 30 / 3</td>
<td>66 / 32 / 3</td>
</tr>
<tr>
<td><strong>No. of disease sites (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>25</td>
<td>31</td>
</tr>
<tr>
<td>2</td>
<td>41</td>
<td>32</td>
</tr>
<tr>
<td>≥3</td>
<td>34</td>
<td>38</td>
</tr>
<tr>
<td><strong>Histological Differentiation (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Well differentiated</td>
<td>82</td>
<td>84</td>
</tr>
<tr>
<td>Moderately differentiated</td>
<td>17</td>
<td>15</td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Prior Treatment (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somatostatin analogues</td>
<td>49</td>
<td>50</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>23</td>
<td>20</td>
</tr>
</tbody>
</table>

Progression Free Survival by Investigator Review

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

148 placebo patients crossed over to everolimus at the time of progression

P value obtained from stratified 1-sided log-rank test
Hazard ratio is obtained from stratified unadjusted Cox model
Everolimus Provided a Durable PFS Benefit

<table>
<thead>
<tr>
<th></th>
<th>Everolimus 10 mg n = 207</th>
<th>Placebo n = 203</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS; Kaplan-Meier estimates [95% CI]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 months</td>
<td>84.0 [78.0-88.4]</td>
<td>58.5 [51.2-65.0]</td>
</tr>
<tr>
<td>6 months</td>
<td>69.5 [62.4-75.5]</td>
<td>31.9 [25.4-38.5]</td>
</tr>
<tr>
<td>12 months</td>
<td>45.6 [37.7-53.1]</td>
<td>15.4 [10.5-21.2]</td>
</tr>
<tr>
<td>18 months</td>
<td>34.2 [25.9-42.7]</td>
<td>8.9 [4.0-16.3]</td>
</tr>
<tr>
<td><strong>Median treatment duration (months)</strong></td>
<td><strong>8.79</strong></td>
<td><strong>3.74</strong></td>
</tr>
<tr>
<td>Median follow-up</td>
<td></td>
<td>17 months</td>
</tr>
</tbody>
</table>

Subgroup PFS Analysis

Yao JC, et al. 35th ESMO Congress 2010; Milan, Italy; Abstract LBA9.

*Independent adjudicated central review.
### Best % Change From Baseline—Waterfall Plots

#### Everolimus (n = 191)

<table>
<thead>
<tr>
<th>Change in % change from baseline</th>
<th>Everolimus n (%)</th>
<th>Placebo n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decrease in best % change from baseline</td>
<td>123 (64.4)</td>
<td>39 (20.6)</td>
</tr>
<tr>
<td>Zero change in best % change from baseline</td>
<td>11 (5.8)</td>
<td>10 (5.3)</td>
</tr>
<tr>
<td>Increase in best % change from baseline</td>
<td>43 (22.5)</td>
<td>112 (59.3)</td>
</tr>
<tr>
<td>% change in target lesion available but contradicted by overall lesion response = PD</td>
<td>14 (7.3)</td>
<td>28 (14.8)</td>
</tr>
</tbody>
</table>

Patients for whom the best % change in target lesions was not available and patients for whom the best % change in target lesions was contradicted by overall lesion response = UNK were excluded from the analysis; percentages above use n as denominator.

Yao JC, et al. 35th ESMO Congress 2010; Milan, Italy; Abstract LBA9.
RADIANT-3: Overall Survival

Kaplan-Meier Median OS
Everolimus       NR
Placebo          36.63 months
HR (95% CI), 0.89 (0.64-1.23)

Patients still at risk, n
Everolimus       207 203 195 189 182 174 163 159 151 147 142 119 91 70 53 39 27 16 7 3 0 0 0 0
Placebo          203 199 195 183 175 168 162 157 150 144 140 118 93 77 59 44 31 20 13 3 2 1 0

RADIANT-3: Treatment-Related Adverse Events >20%

<table>
<thead>
<tr>
<th>Treatment duration: median (range)</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><strong>Everolimus: 8.79 mos (0.25 - 27.47)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo: 3.74 mos (0.01 – 37.79)</td>
<td></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>Diarrhoea</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 oedema</td>
<td>41 (20)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>40 (20)</td>
<td>0</td>
</tr>
</tbody>
</table>

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

RADIANT-3 Summary

• RADIANT-3 enrolled 410 patients with advanced pNET, the largest-ever placebo-controlled phase III clinical trial in this patient population

• Everolimus provided a statistically and clinically significant improvement in median PFS by 6.4 month compared to placebo

• Everolimus provided a durable benefit; 18-mo PFS rate of 34% vs. 9% placebo

• Consistent benefit seen with everolimus across all subgroups

• Everolimus has an acceptable safety profile

RADIANT-2 Study Design

Phase III Randomised, Double-Blind, Placebo-Controlled Trial

Patients with advanced NET and a history of secretory symptoms (N = 429)
- Advanced low- or intermediate-grade NET
- Radiologic progression ≤12 months
- History of secretory symptoms (flushing, diarrhoea)
- Prior anti-tumour therapy allowed
- WHO PS ≤2

Primary Endpoint:
- PFS
  Statistical boundary = .0246

Secondary Endpoints:
- OS
- ORR
- Biomarkers
- Safety
- PK

Enrollment January 2007-March 2008
PD = progressive disease; ORR = overall response rate; PK = pharmacokinetics


Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Everolimus + Oct LAR n = 207</th>
<th>Placebo + Oct LAR n = 203</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>60 (22-83)</td>
<td>60 (27-81)</td>
</tr>
<tr>
<td>Male:Female (%)</td>
<td>45:55</td>
<td>58:42</td>
</tr>
<tr>
<td>WHO PS (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>55</td>
<td>66</td>
</tr>
<tr>
<td>1/2*</td>
<td>39/6</td>
<td>29/5</td>
</tr>
<tr>
<td>Primary site (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small intestine</td>
<td>51</td>
<td>53</td>
</tr>
<tr>
<td>Lung*</td>
<td>15</td>
<td>5</td>
</tr>
<tr>
<td>Colon</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Pancreas</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Liver</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Prior somatostatin analogues</td>
<td>80</td>
<td>78</td>
</tr>
<tr>
<td>Prior systemic anti-tumour therapies</td>
<td>46</td>
<td>38</td>
</tr>
<tr>
<td>Chemotherapy*</td>
<td>35</td>
<td>26</td>
</tr>
<tr>
<td>Immunotherapy</td>
<td>13</td>
<td>9</td>
</tr>
<tr>
<td>Targeted therapy</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Other</td>
<td>10</td>
<td>12</td>
</tr>
</tbody>
</table>

*Statistically significant for imbalance $P<.05$. One missing PS in placebo arm

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 [0.591.00]
$P$ value = .026 (pre-specified boundary = .0246)

Total events = 223
Censoring times
- E + O (n/N = 103/216)
- P + O (n/N = 120/213)

123 placebo + octreotide LAR patients crossed over at the time of progression

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

PFS by Local Investigator Review

Kaplan-Meier median PFS
Everolimus + Octreotide LAR: 12.0 months
Placebo + Octreotide LAR: 8.6 months
Hazard ratio = 0.78; 95% CI [0.620.98]
P value = .018

Total events = 284
Censoring times
E + O (n/N = 128/216)
P + O (n/N = 156/213)

Number of patients still at risk
E + O
216 199 167 129 119 100 81 74 68 62 51 40 32 24 18 11 4 2 1 1 0
P + O
213 201 159 121 114 92 75 72 64 56 50 41 27 21 11 10 4 1 0 0

P value is obtained from the one-sided log rank test
Hazard ratio is obtained from unadjusted Cox model
E + O = Everolimus + Octreotide LAR
P + O = Placebo + Octreotide LAR

PFS Comparison of Primary Analysis and Preplanned Supportive Analysis

<table>
<thead>
<tr>
<th></th>
<th>Hazard ratio (95% CI)</th>
<th>P value</th>
<th>Everolimus + Oct LAR</th>
<th>Placebo + Oct LAR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Central</strong>&lt;sup&gt;*&lt;/sup&gt; (223 events)</td>
<td>0.77 (0.59-1.00)</td>
<td>0.026</td>
<td>16.4</td>
<td>11.3</td>
</tr>
<tr>
<td><strong>Local</strong> (284 events)</td>
<td>0.78 (0.62-0.98)</td>
<td>0.018</td>
<td>12.0</td>
<td>8.6</td>
</tr>
<tr>
<td><strong>IPCW</strong>&lt;sup&gt;†&lt;/sup&gt;</td>
<td>0.60 (0.44-0.84)</td>
<td>0.0014</td>
<td>13.8</td>
<td>8.3</td>
</tr>
</tbody>
</table>

* Independent adjudicated central review committee

† Inverse probability of censoring weighting (IPCW) analysis was conducted to correct for informative censoring (which resulted in a loss of PFS events) and for imbalances in baseline characteristics. IPCW is a reliable and validated methodology used in other large phase III trials confounded by crossover.

# Everolimus + Octreotide LAR in Carcinoids Subgroup PFS Analysis (RADIANT-2)

## Subgroup PFS Analysis


<table>
<thead>
<tr>
<th>Subgroup</th>
<th>N</th>
<th>Favours E+O</th>
<th>Favours P+O</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary analysis*</td>
<td>429</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Investigator review</td>
<td>429</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age group</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 65 yr</td>
<td>286</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 65 yr</td>
<td>143</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>221</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>208</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>WHO PS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>251</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 or 2</td>
<td>176</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Primary tumour site</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small intestine</td>
<td>224</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>44</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colon</td>
<td>28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>132</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Prior long-acting SSA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>339</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>90</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Independent adjudicated central review
HR = Everolimus + Octreotide/Placebo + Octreotide
Unstratified Cox model was used to obtain hazard ratio
Percentage Tumour Shrinkage from Baseline

Everolimus (n=200)

Placebo (n=203)

<table>
<thead>
<tr>
<th>E + O n (%)</th>
<th>P + O n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase in size of target lesions from baseline</td>
<td>43 (22)</td>
</tr>
<tr>
<td>No change in size of target lesions from baseline</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Decrease in size of target lesions from baseline</td>
<td>150 (75)</td>
</tr>
<tr>
<td>Change in size of target lesion was available but contradicted by overall lesion response of PD</td>
<td>4 (2)</td>
</tr>
</tbody>
</table>

E + O = Everolimus + Octreotide LAR  P + O = Placebo + Octreotide LAR

RADIANT-2: Multivariate Analysis of PFS

<table>
<thead>
<tr>
<th>Variable</th>
<th>Groups</th>
<th>n</th>
<th>HR (95% CI), months</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>E+O</td>
<td>216</td>
<td>0.62 (0.51-0.87)</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td>P+O</td>
<td>213</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHO PS</td>
<td>0</td>
<td>257</td>
<td>0.69 (0.52-0.90)</td>
<td>0.006</td>
</tr>
<tr>
<td></td>
<td>≥1</td>
<td>227</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline CgA</td>
<td>Non-elevated</td>
<td>138</td>
<td>0.47 (0.34-0.65)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Elevated</td>
<td>282</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone involvement</td>
<td>Yes</td>
<td>59</td>
<td>1.52 (1.06-2.18)</td>
<td>0.020</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>367</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung as primary site</td>
<td>Yes</td>
<td>44</td>
<td>1.55 (1.01-2.36)</td>
<td>0.044</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>385</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Baseline CgA levels, WHO PS, lung as primary site, and bone involvement are important prognostic factors.

Non-elevated, ≤2× ULN; elevated, >2× ULN.
*Two-sided from Cox proportional hazards model, with variables selected using stepwise regression.

PFS was Determined Adjusted to Risk for Progression

- Baseline CgA levels, WHO PS, lung as primary site, and bone involvement were important prognostic factors
- Exploratory analyses adjusted for these prognostic factors indicated persistent significant benefit for everolimus + octreotide LAR therapy compared with placebo + octreotide LAR

![Graph showing comparison between Everolimus + octreotide LAR and Placebo + octreotide LAR](image)

Adjusted for covariates:
Hazard ratio, 0.62; 95% CI, 0.51-0.87
\( P = 0.003 \) (2-sided from Cox model)

RADIANT-2 Updated Safety Results – Treatment-Related Adverse Events

- At the time of the updated safety analysis, median follow up was 31.1 months
- Median exposure to everolimus + octreotide LAR increased by 8.2 patient years over initial analysis
- Overall frequency of treatment-related AEs remained constant
- Overall frequency of treatment-related grade 3/4 AEs remained the same

### Treatment-Related AEs (Grade 3 or 4) in ≥5% of Patients

<table>
<thead>
<tr>
<th>Adverse Event, Grade 3/4, %</th>
<th>Original Study Cutoff April 2, 2010, %</th>
<th>Safety Update July 2, 2010, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>E+O n = 215</td>
<td>P+O n = 211</td>
</tr>
<tr>
<td></td>
<td>Gr 3</td>
<td>Gr 4</td>
</tr>
<tr>
<td>All</td>
<td>40.5</td>
<td>4.7</td>
</tr>
<tr>
<td>Fatigue</td>
<td>6.5</td>
<td>0</td>
</tr>
<tr>
<td>Stomatitis*</td>
<td>6.5</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>6.0</td>
<td>0</td>
</tr>
<tr>
<td>Infections*</td>
<td>4.7</td>
<td>0.5</td>
</tr>
<tr>
<td>Hyperglycaemia</td>
<td>5.1</td>
<td>0</td>
</tr>
</tbody>
</table>

*Related toxicities grouped for calculations
E + O = everolimus + octreotide LAR
P + O = placebo + octreotide LAR

RADIANT-2 Summary

- Everolimus + octreotide LAR demonstrated a clinically meaningful 5.1 month prolongation of median PFS (HR = 0.77; \( P = 0.026 \)); the Hazard Ratio did not reach statistical significance (pre-specified \( P = 0.0246 \))

- Local assessment supports activity of everolimus + octreotide LAR with a similar HR of 0.78 (\( P = 0.018 \))

- Pre-specified statistical analysis (IPCW) adjusting for different censoring patterns, loss of power and baseline imbalances demonstrates a consistent benefit (HR = 0.60)

- Everolimus + octreotide LAR was associated with tumour shrinkage and stabilisation
RADIANT-2 Subgroup Supports PROMID Results

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Treatment Arm</th>
<th>Median PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROMID¹</td>
<td>Treatment-naïve midgut NET, n = 42</td>
<td>Octreotide LAR 30 mg</td>
<td>14.3 months</td>
</tr>
<tr>
<td>RADIANT-2²</td>
<td>SSA-naïve, progressing NET, n = 90</td>
<td>Octreotide LAR 30 mg + Placebo</td>
<td>13.6 months</td>
</tr>
</tbody>
</table>

LX1606 (Telotristat Etiprate) – Inhibitor of serotonin synthesis
Telotristat Etiprate in Patients with Carcinoid Syndrome

\[ N = 15 \]

**Therapy:** Telotristat Etiprate 150-500 mg tid.

**Results:**
- 44.5% decrease in BM
- 72% decrease in U-5HIAA
- 75% adequate to relief

Well tolerated treatment

*Pavel et al. ENETS Conference Barcelona 2013*
Treatment Algorithm for NET (modified by results from Nordic NET-study)

Metastatic NET

Debulking Surgery embolization Radioembolization RF

WHO Grade I
Ki-67 <2%
(Ki-67 <5% PNET)

SMS α-IFN Everolimus PRRT Combinations

WHO Grade II
Ki-67 2-20%
(Ki-67 5-20% PNET)

Streptozotocin+5FU Everolimus Sunitinib Temozolomide + capecitabine PRRT

WHO Grade III
Ki-67 >20%

Ki-67 <55%
(Ki-67 5-20% PNET)

Temozolomide + capecitabine + Avastin (Folfox) (Folfiri)

Ki-67 >55%

Cispl/carbo + etoposide

SMS with functioning tumors
Improving Access to Specialized Care Improves Patient Outcomes

- Multidisciplinary centers are associated with improved survival for patients with NETs
- Median survival of patients with metastatic NETs treated at “centers of excellence”* is ≥3 times higher than median survival of patients with NETs in SEER database

*Centers of Excellence = Uppsala Center, Sweden; the Moffitt Cancer Center, Tampa, FL, USA.

Thank you!

Centre of Excellence Endocrine Tumors, Uppsala University
http://www.endocrinetumors.org/