Targeting the PI3K/AKT/mTor pathway in pancreatic NET (pNET)

Marianne Pavel

Charité University Medicine Berlin, Campus Virchow Klinikum

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Sitges-Barcelona, March 1, 2014
Overview

- Special Features & Classification
- Rationale to use mTOR inhibitors in pNET
- Results from Phase II/III clinical trials
- Therapeutic algorithm (ESMO Guidelines)
- Future perspectives
Topographic Distribution of 35,825 NET US SEER Database

Incidence: 4-5/ 100000 population

- Rectum: 17.2
- Jejunum/ileum: 13.4
- Pancreas: 6.40
- Stomach: 6.00
- Colon: 4.00
- Duodenum: 3.80
- Cecum: 3.20
- Appendix: 3.00
- Liver: 0.80

Pancreatic NET

- Most pNET are sporadic; 10-30% occur within hereditary syndromes (MEN-1, VHL, TSC)
- 1/3 functionally active NET
  - Insulinoma, Gastrinoma, VIPoma, Glucagonoma
  - Clinical features + elevated circulating biomarker
- Diagnosis is based on histopathology / IHC
  - Chromogranin A, Synaptophysin, optionally other markers
- High density of somatostatin receptors
- The majority (60-76%) presents with metastatic disease at diagnosis (exception insulinoma); variable growth behaviour
- 5 yr survival rates in stage IV disease 36-50%

# Differentiation and Grading of NEN

All neuroendocrine neoplasms (NEN) have a malignant potential

<table>
<thead>
<tr>
<th>Grading</th>
<th>Mitosis (10HPF)(^a)</th>
<th>Ki-67 Index (%)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>&lt; 2</td>
<td>≤ 2</td>
</tr>
<tr>
<td>G2</td>
<td>2 – 20</td>
<td>&gt; 2 – 20</td>
</tr>
<tr>
<td>G3</td>
<td>&gt; 20</td>
<td>&gt; 20</td>
</tr>
</tbody>
</table>

\(^a\)10 HPF: high power field = 2cm\(^2\), at least 40 Fields (40x magnification, areas of highest mitotic density)

\(^b\)MIB-1 Antibody in % of 2000 Tumor cells in "hot spot" – areas

1. Neuroendocrine Tumor G1 NET G1 (Carcinoid)\(^b\)
2. Neuroendocrine Tumor G2 NET G2
3. Neuroendocrine carcinoma NEC G3 (large cell or small cell type)\(^b, c\)

<table>
<thead>
<tr>
<th>WHO 1980</th>
<th>WHO 2000</th>
<th>WHO 2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Carcinoid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grading</td>
<td>Mitosis (10HPF)</td>
<td>Ki-67 Index (%)</td>
</tr>
<tr>
<td>III. Carcinoid-Adenocarcinoma</td>
<td>5. Tumor like lesion (TLL)</td>
<td>5. Hyperplastic and preneoplastic Lesions</td>
</tr>
<tr>
<td>IV. Pseudotumorous Lesions</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^b\) MIB-1 Antibody in % of 2000 Tumor cells in "hot spot" – areas
Prognostic impact of Grading and Staging - e.g. Pancreatic NEN (n=926 Patients)

TNM Staging of Neoplasms of the Endocrine Pancreas: Results From a Large International Cohort Study


### G2 NETs - Distribution of grading according to primary tumor site

<table>
<thead>
<tr>
<th>Author, year</th>
<th>n</th>
<th>Grading</th>
<th>&lt;2</th>
<th>2-20</th>
<th>&gt;20</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pancreatic NET</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreatic NET: G2 &gt; G1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pape, 2008</td>
<td>158</td>
<td>28</td>
<td>54</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Scarpa, 2010</td>
<td>237</td>
<td>55</td>
<td>36</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Pancreatic NET: G2 &gt; G1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rinke, 2009</td>
<td>81</td>
<td>95</td>
<td>5</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Jann, 2011</td>
<td>189</td>
<td>62</td>
<td>32 **</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Panzuto, 2011</td>
<td>114</td>
<td>57</td>
<td>43</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Intestinal NET: G1 > G2**

Grading assessed in either primary tumor or metastases

* >2->10%; **Midgut and hindgut
Activation of the Akt/mTOR pathway during tumorigenesis

RIP-Tag2 transgenic mouse model

- Develops pancreatic NET

Pancreas dissection
WT: 5 wk
RIP-Tag2: 5; 7.5; 12 wk

Immunostaining with Ab indicative of activation of EGFR, mTOR and Akt:
- Phosphorylated EGFR
- Phosphorylated S6 ribosomal protein
- Phosphorylated Akt

Progressive activation of the Akt/mTOR and EGFR signaling pathways during pancreatic tumorigenesis

Chiu, Nozawa, and Hanahan J Clin Oncol 2010
<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Genes</th>
<th>Tumors</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Multiple endocrine Neoplasia Type 1 (MEN-1)</strong></td>
<td>MENIN</td>
<td>Pituitary; Parathyroid Pancreas; Lungs Thymus</td>
<td>Menin regulates gene transcription</td>
</tr>
<tr>
<td><strong>Tuberous Sclerosis</strong></td>
<td>TSC-2 (16p13.3)</td>
<td>Pancreas</td>
<td>Loss leads to constitutive activation of mTOR</td>
</tr>
<tr>
<td><strong>Neurofibromatosis</strong></td>
<td>NF-1 (17q11.2)</td>
<td>Duodenum Mediastinum</td>
<td>Loss leads to constitutive activation of mTOR</td>
</tr>
<tr>
<td><strong>Von Hippel Lindau</strong></td>
<td>VHL (3p26-p25)</td>
<td>Pancreas</td>
<td>Loss leads to HIF activity</td>
</tr>
</tbody>
</table>

Yao et al, Best Practice & Research Clinical Endocrinology & Metabolism 2007: 21, 1
Mutations in MEN1 and DAXX/ATRX Genes are associated with better prognosis

Mutations in the mTOR pathway: PTEN, TSC2, and PIK3CA

<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>DAXX, 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>TGFBR1, SMAD3, SMAD4</td>
<td>0%</td>
<td>38%</td>
</tr>
</tbody>
</table>

Jiao et al, Science 2011
Pancreatic NET: Expression Profiling Evidences a Role for AKT-mTOR Pathway

**TSC2 Expression**
- 72 primary PETs, 10 normal pancreatic samples
- High-level TSC2 vs. Low-level TSC2
- Overall Survival
- Progression-free Survival

**PTEN Expression**
- High-level PTEN vs. Low-level PTEN
- Progression-free Survival
- Time (yr)


PTEN as a prognostic Marker in NET; Kausch et al, HMR 2011

High expression of MTOR or its downstream targets p-RPS6KB1, p-RPS6, or p-EIF4EBP1 was associated with adverse clinical outcomes; Qian et al, J Clin Oncol 2013
Clinical Trials with Everolimus in neuroendocrine Tumors

Pancreatic NET
- US 52, n=30
- RADIANT-1; n=160
- RADIANT-3; PCT; n=410
- COOPERATE-2, n=280, ongoing


Non-pancreatic NET
- US-52, n=30
- RADIANT-2, PCT, (NET with carcinoid syndrome), n=429
- RAMSETE (NF non-pancreatic), n=60
- RADIANT-4 (GI/ lung), n=280, ongoing

## Results from phase II clinical trials with mTOR inhibitors in advanced NET/pNET

<table>
<thead>
<tr>
<th>Author</th>
<th>No of pts.</th>
<th>Tumor type</th>
<th>Therapy</th>
<th>Prior PD</th>
<th>ORR (%)</th>
<th>PFS (months)</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duran et al, Br J Cancer 2006</td>
<td>37</td>
<td>15 pNET 21”Carcinoid”</td>
<td><strong>Temsiprolimus</strong> 25 mg iv/wk</td>
<td>Yes</td>
<td>5.6</td>
<td>6.0#</td>
<td>#TTP; 54% SD</td>
</tr>
<tr>
<td>Yao et al, J Clin Oncol 2008</td>
<td>60</td>
<td>30 pNET 30 Carcinoid</td>
<td><strong>Everolimus</strong> 5 or 10 mg/d + <strong>Octreotide</strong> LAR 30 mg</td>
<td>No</td>
<td>27 17</td>
<td>12.5 15.8</td>
<td>10 mg superior to 5 mg (PFS) 70% SD</td>
</tr>
<tr>
<td>Yao et al, J Clin Oncol 2010</td>
<td>160</td>
<td>RADIANT 1 pNET, 2 Strata (I/II) After failure of chemotherapy</td>
<td><strong>Everolimus</strong> 10 mg/d (I) <strong>Everolimus + Octreotide</strong> LAR 30 mg (II)</td>
<td>Yes</td>
<td>9.6 (I) 68% SD</td>
<td>9.7 16.7</td>
<td>n=115: Everolimus (I) n=45: Everolimus+ Octreotide LAR (II)</td>
</tr>
</tbody>
</table>
Predictive value of Biomarkers?

Response to Everolimus in pNET by early decrease of Chromogranin A

Median PFS
- Early response = 13.3 mos.
- No early response = 7.5 mos.

HR=0.25
95% CI: 0.13-0.51
p=0.00004
RADIANT-3: Study Design

Phase III, Double-Blind, Placebo-Controlled Trial

Patients with advanced and progressive pNET, N = 410

Stratified by:
- WHO PS
- Prior chemotherapy

1:1

Everolimus 10 mg/d + best supportive care\(^1\)
\[ n = 207 \]

Placebo + best supportive care\(^1\)
\[ n = 203 \]

Crossover

Treatment until disease progression

Multiphasic CT or MRI performed every 12 weeks

Primary Endpoint: PFS
Secondary Endpoints: OS, ORR, biomarkers, safety, pharmacokinetics (PK)

1. Concurrent somatostatin analogues allowed
### RADIANT-3: Prior Therapies

<table>
<thead>
<tr>
<th>Therapy Type</th>
<th>Everolimus (n = 207) %</th>
<th>Placebo (n = 203) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-tumor medication</td>
<td>58</td>
<td>58</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Targeted therapy</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Immunotherapy</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Hormonal therapy</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>11</td>
<td>14</td>
</tr>
<tr>
<td>Somatostatin analogs</td>
<td>49</td>
<td>50</td>
</tr>
</tbody>
</table>

**Progression free survival**

*Everolimus vs. Placebo in pancreatic NET*

Kaplan-Meier medians PFS
- **Everolimus:** 11.0 months
- **Placebo:** 4.6 months

Hazard ratio is obtained from stratified unadjusted Cox model

\[
HR = 0.35; \ 95\% \ CI \ [0.27-0.45]
\]

\[
P \text{ value: } <.0001
\]

No. of patients still at risk

<table>
<thead>
<tr>
<th></th>
<th>Everolimus (n/N = 109/207)</th>
<th>Placebo (n/N = 165/203)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>207</td>
<td>203</td>
</tr>
<tr>
<td>1</td>
<td>189</td>
<td>177</td>
</tr>
<tr>
<td>2</td>
<td>153</td>
<td>98</td>
</tr>
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<td>3</td>
<td>126</td>
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<td>4</td>
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<td>5</td>
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<td>6</td>
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<td>16</td>
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<td>7</td>
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<td>8</td>
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<td>11</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>12</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>13</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>14</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>15</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**PFS rate (18 mos.)**
- **Everolimus:** 34.2%
- **Placebo:** 8.9%

*by Investigator Review*

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

### Everolimus vs Placebo in progressive pancreatic NET (RADIANT-3) Subgroup Analysis

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>No.</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local investigator review</td>
<td>410</td>
<td>0.35 (0.27–0.45)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Central adjudicated review</td>
<td>410</td>
<td>0.34 (0.26–0.44)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Previous chemotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>189</td>
<td>0.34 (0.24–0.49)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No</td>
<td>221</td>
<td>0.41 (0.29–0.58)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WHO performance status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>279</td>
<td>0.39 (0.28–0.53)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1 or 2</td>
<td>131</td>
<td>0.30 (0.20–0.47)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤65 yr</td>
<td>299</td>
<td>0.39 (0.29–0.53)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt;65 yr</td>
<td>111</td>
<td>0.36 (0.22–0.58)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>227</td>
<td>0.41 (0.30–0.58)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female</td>
<td>183</td>
<td>0.33 (0.23–0.48)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>322</td>
<td>0.41 (0.31–0.53)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Asian</td>
<td>74</td>
<td>0.29 (0.15–0.56)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Region</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>America</td>
<td>185</td>
<td>0.36 (0.25–0.52)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Europe</td>
<td>156</td>
<td>0.47 (0.32–0.69)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Asia</td>
<td>69</td>
<td>0.29 (0.14–0.56)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Previous long-acting SSA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>203</td>
<td>0.40 (0.28–0.57)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No</td>
<td>207</td>
<td>0.36 (0.25–0.51)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tumor grade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Well differentiated</td>
<td>341</td>
<td>0.41 (0.31–0.53)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Moderately differentiated</td>
<td>65</td>
<td>0.21 (0.11–0.42)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Yao et al, NEJM 2011
Everolimus versus Placebo: Best Response of Target Lesions (% Change)

Objective Tumor remissions (Everolimus/Placebo): 5% versus 2%

Any tumor shrinkage: 64 versus 21%

RADIANT-3: overall survival

Kaplan–Meier median
Everolimus, NA
Placebo, NA

Hazard ratio, 1.05 (95% CI, 0.71–1.55)
p=0.59 by one-sided log-rank test

Cross-over Design
80% of the patients in the placebo arm received everolimus after progression

CI, confidence interval; NA, not available.
## Antiproliferative Therapy in pancreatic G1/G2 GEP-NET

### Somatostatin analogs
- Octreotide LAR, Lanreotide AG
- Lanreotide AG vs. Placebo (CLARINET-Study positive: enteropancre. NET, -10% Ki67; ESMO 2013)

<table>
<thead>
<tr>
<th>ORR</th>
<th>PFS (Mon)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5%</td>
<td>&gt;27</td>
</tr>
</tbody>
</table>

### Interferon alpha

<table>
<thead>
<tr>
<th>ORR</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10%</td>
</tr>
</tbody>
</table>

### Chemotherapy
- Streptozotocin + 5-Fluorouracil: ca. 30-40%
- Temozolomide + Thalidomid or TEM+/- Capecitabine: 45-70% (prosp. /retrosp.)

<table>
<thead>
<tr>
<th>ORR</th>
<th>PFS (Mon)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9-18</td>
<td>-18</td>
</tr>
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</table>

### Everolimus, Sunitinib

<table>
<thead>
<tr>
<th>ORR</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 bzw 9 %</td>
</tr>
</tbody>
</table>

### Peptide radioreceptor therapy

<table>
<thead>
<tr>
<th>ORR</th>
<th>PFS (Mon)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9-40% RR (v.a. retrosp.)</td>
<td>?</td>
</tr>
</tbody>
</table>

Pancreatic NET
NCCN Guidelines 1.2014

MANAGEMENT OF LOCOREGIONAL UNRESECTABLE DISEASE AND/OR DISTANT METASTASES

If complete resection possible

- Resect metastases + primary
- Clinically significant progressive disease, see below

Locoregional unresectable disease and/or Distant metastases

- Asymptomatic, low tumor burden and stable disease
  - Observe with markers and scans every 3-12 mo
  - Clinically significant progressive disease, see below
  - Everolimus (10 mg/d) or Sunitinib (37.5 mg/d) or Cytotoxic chemotherapy

- Symptomatic or Clinically significant tumor burden or Clinically significant progressive disease
  - Manage clinically significant symptoms as appropriate
  - Hepatic regional therapy (arterial embolization, chemoembolization, radioembolization (category 2B), ablative therapy)
  - Cytoreductive surgery (category 2B)
  - Consider octreotide if not already receiving (category 2B)
Future Perspectives

- Drugs to overcome resistance to mTOR inhibitors
- Combination therapies
  - Angiogenesis inhibitors (Bevacizumab)
  - Somatostatin analogs (Pasireotide)
- Sequencing of therapies
- Evaluation in NEC G3
PI3 Kinase-AKT-mTOR Pathway and Inhibitors

IGF-R1 Ab/SSA

PI3Kinase Inhibitors

Akt Inhibitors

MK-2206, phase II

COOPERATE I/II studies

Yap et al Curr Opin Pharmacol 2008
BEZ235- Study in pNET after failure of Everolimus

**Patient Population**
- Advanced, G1 or G2 pNET
- Refractory to mTORi
- Measurable disease
- No more than 3 prior systemic lines

**Efficacy Open label**
- BEZ235 400 mg bid (n=30)

**Randomized placebo controlled**
- Criteria fulfilled allowing stage 2
  - BEZ235 400 mg bid + BSC
  - Placebo + BSC
- Criteria fulfilled allowing cross-over
  - BEZ235 400 mg bid + BSC

**Screening Phase**
- **Stage 1**
- **Stage 2**
- **Cross-Over (if applicable)**

**BEZ235 – dual PI3K/mTOR Inhibitor**

Courtesy R Tavorath, Novartis, modified
CBEZ235Z2401: BEZ235 vs Everolimus in progressive pNET (Phase II study)

- Patients with advanced histologically confirmed pNET
  - No prior everolimus

Stratified by:
- Baseline NSE and/or CgA level
- Concurrent somatostatin analogue treatment

Randomize 1:1

BEZ235 400 mg bid
n = 70

Everolimus 10 mg qd
n = 70

Multi-phasic CT or MRI performed every 12 weeks

Treatment until disease progression, and toxicity

Discontinuation of treatment due to:
- PD
- Unacceptable AEs
- Consent withdrawal
- Others specified

Follow-up for:
- Efficacy
- Safety (till 30 days post treatment)
- Survival

The targeted FPFV Sept 30, 2012

NSE: Neuron specific enolase
CgA: Chromogranin A

Courtesy R Tavorath, Novartis
Candidates to combine with mTOR inhibitors in NET

Current clinical trials

- Somatostatin analogues
  - Pasireotide (COOPERATE-1, Berlin; NCT00804336; COOPERATE-2)

- IGFR-1 inhibitors (IMC-A12+ OCT + RAD001; NCT01204476, MDACC)

- EGFR inhibitors (RAD001 + Erlotinib; NCI NCT00843531, UCSF)
  - Erlotinib, Gefitinib

- Angiogenesis inhibitors (RAD001 + Bevacizumab; NCI CALGB80701, Boston)

- Akt inhibitors (MK2206: NCT01169649, MSKCC)

- Phosphatidylinositol 3-kinase inhibitors upcoming
Everolimus or Everolimus + SSA?

- **RADIANT-1 Study** (pancreatic NET, 2 Strata, **no comparative study**!):
  - mPFS **9.7 vs. 16.7 mo.** without/ with SSA

- **COOPERATE-2** (pancreatic NET):
  - Everolimus vs.
  - Everolimus + Pasireotide LAR in progressive pNET
  - Study closed, ongoing, results pending
Temsirilimus (TEM) and Bevacizumab (BEV) in pNET: multicenter Phase II Study

- 55 patients with progressive well to moderately differentiated pNET
- Progression (RECIST) within 7 Months
- **Primary Endpoint:** ORR, 6 Mo. PFS
- Temsirolimus 25 mg iv d 1,8,15,22;
- Bevacizumab 10 mg/kg iv d 1,15

<table>
<thead>
<tr>
<th>PR</th>
<th>6 mo. PFS</th>
<th>12 mo. PFS</th>
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<tbody>
<tr>
<td>37%</td>
<td>80%</td>
<td>49%</td>
</tr>
<tr>
<td>(20/55)</td>
<td>(44/55)</td>
<td>(24/49)</td>
</tr>
</tbody>
</table>

Most frequent Grade 3-4 adverse events: Hypertension (18%), Hyperglycemia (13%), Fatigue (11%). Leukopenia (9%), Headaches (9%), Proteinuria (7%), Hypokalemia (7%)

T Hobday, et al, ASCO Annual Meeting 2013
Multicenter phase II trial of temsirolimus (TEM) and bevacizumab (BEV) in pancreatic neuroendocrine tumor (pNET)

Progression Free Survival

- Median (95% CI): 11.73 (11.07-15.64)

Waterfall Plot of Best Response

1) Excludes 2 cancels as well as 4 patients who have no post baseline measurements.
2) PH1573 progressed via symptomatic deterioration but the actual tumor measurements qualified as stable disease (SD), so he is displayed as SD in this plot.

CALGB Trial (80701):
Everolimus vs. Everolimus + Bevacizumab

T Hobday, et al, ASCO Annual Meeting 2013
Sequencing mTOR inhibitor and systemic chemotherapy (SEQTOR trial)

1st course                  Interval                  2nd course

Arm A: **Everolimus**
       (10 mg/ Tag)

Progression

Arm B: **STZ-5FU**
       (Moertel or Uppsala)

Study supported by the European Neuroendocrine Tumor Society (ENETS)
Study lead: Ramon Salazar, Barcelona, GTE group
Any role of mTOR inhibitors in NEC G3?
Components of the mTOR pathway are expressed in NEC G3

<table>
<thead>
<tr>
<th>p-mTOR</th>
<th>n (%)</th>
<th>OS (mo)</th>
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</thead>
<tbody>
<tr>
<td>Positive</td>
<td>32</td>
<td>9.4</td>
</tr>
<tr>
<td>Negative</td>
<td>68</td>
<td>23.7</td>
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</table>

<table>
<thead>
<tr>
<th>p-eIF4E</th>
<th>n (%)</th>
<th>OS (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>76</td>
<td></td>
</tr>
</tbody>
</table>

N=27

Clinical Trials in NEC G3
- Everolimus 2nd line (EVINEC)
- Everolimus + Temozolomide (NORDIC NEC Study)
- EVE+Paclitaxel +Carboplatin (Large cell NEC, lung)

Heetfeld et al, unpubl.
Summary & Conclusions

- The PI3K/AKT/mTOR pathway is activated in pNET (preclinical models, hereditary syndromes, human tumor tissue)
- Mutations of the PI3K/AKT/mTOR pathway are rare; no genotype phenotype correlations yet
- ORR with mTOR inhibitors are low, prolongation of PFS with Everolimus by 6 months vs Placebo in pNET
- Some patients may have a Durable benefit (1/3 > 18 mo.)
- Early drop of circulating biomarkers is associated with more favourable PFS, however reliable and validated response predictors are lacking
Summary & Conclusions

- Everolimus is one of several therapeutic options in pNET; the place in the treatment algorithm remains unclear (SEQTOR trial)
- To improve the outcome drugs to overcome resistance to mTOR inhibitors and combination therapies are further explored (combination with SSA or Bevacizumab look promising)
- Molecular markers need to be identified to predict response to therapy
Thank you!