New Treatments for Neuroendocrine Cancers

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Disclosures

- Contracted research support from:
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  Pharmaceutical Research Associates
- Stock ownership: Seattle Genetics (spouse)
Topics

- NET 101: the basics
- Biological “targets”
  - Somatostatin receptors
  - mTOR
  - Angiogenesis
- Chemotherapy
- Liver directed options
“Rare-omas”

- Incidence is low
  # diagnosed per year per 100,000 people

<table>
<thead>
<tr>
<th>Site</th>
<th>Incidence (per 100,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>1.35</td>
</tr>
<tr>
<td>Thymus</td>
<td>0.02</td>
</tr>
<tr>
<td>Stomach</td>
<td>0.30</td>
</tr>
<tr>
<td>Small intestine</td>
<td>0.86</td>
</tr>
<tr>
<td>Colon</td>
<td>0.36</td>
</tr>
<tr>
<td>Appendix</td>
<td>0.15</td>
</tr>
<tr>
<td>Rectum</td>
<td>0.86</td>
</tr>
<tr>
<td>Pancreas</td>
<td>0.32</td>
</tr>
<tr>
<td>Liver</td>
<td>0.04</td>
</tr>
<tr>
<td>Other / unknown</td>
<td>0.74</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>5.00</strong></td>
</tr>
</tbody>
</table>

Increasing Incidence

Yao et al JCO ‘08
Increasing Incidence

Yao et al JCO ‘08

Octreotide Approved

Not really that rare…

More Prevalent Than Stomach and Pancreatic Cancer Combined 1,2
**Imaging Issues with NETs**

- Non-contrast scan
- Arterial phase scan
- Venous phase scan

**NET Path: Grading System**

<table>
<thead>
<tr>
<th>NET (ENETS, WHO)</th>
<th>Grade</th>
<th>Designation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2 mitoses/10hpf AND &lt;3% Ki67 index</td>
<td>Low grade</td>
<td>Well-differentiated</td>
</tr>
<tr>
<td>2-20 mitoses/10hpf OR 3-20% Ki67 index</td>
<td>Intermediate grade</td>
<td></td>
</tr>
<tr>
<td>&gt;20 mitoses/10hpf OR &gt;20% Ki67 index</td>
<td>High grade</td>
<td>Poorly-differentiated</td>
</tr>
</tbody>
</table>

NET Biology

- 5 somatostatin receptors (SSTR_{1-5})
- 80% NETs over-express SSTR_2, followed by SSTR_1 and SSTR_5
- Octreotide has high affinity for SSTR_2

Radiolabelled somatostatin: imaging
Radiolabelled somatostatin: imaging

Octreoscan image


Radiolabelled somatostatin: imaging

\(^{111}\text{In-octreotide Octreoscan}\)

\(^{68}\text{Ga-DOTATATE PET}\)
Targeting the Somatostatin Receptors

<table>
<thead>
<tr>
<th>Function</th>
<th>SST₁</th>
<th>SST₂</th>
<th>SST₃</th>
<th>SST₄</th>
<th>SST₅</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antisecretory</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Anti-angiogenic</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Antiproliferative/Inhibition of cell cycle</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Induction of apoptosis</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
</tbody>
</table>

Adapted from Susini C, Buscail L and Weckbecker G, Lewis I, Albert R, et al.¹


Somatostatin Analogs: Octreotide

PROMID STUDY IN MIDGUT CARCINOID

85 patients with well-differentiated metastatic midgut NETs

Randomize

Octreotide LAR 30 mg IM q4wks N=42
Placebo IM q4wks N=43

Primary Endpoint
- Time to Progression

Secondary Endpoints
- Overall Survival
- Response Rates

Time to Progression

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Octreotide</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion without high risk events</td>
<td>0.50</td>
<td>0.44</td>
</tr>
</tbody>
</table>

p=0.000072, HR 0.34 (95% CI 0.20-0.59)

Overall Survival

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Octreotide</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS not yet reached</td>
<td>97.4 months (not reached)</td>
<td>76.7 months</td>
</tr>
</tbody>
</table>

Arnold, GI ASCO 2009, abstract #121.
Somatostatin Analogs: Lanreotide

CLARINET STUDY IN GEP-NETS (MIDGUT + PANCREATIC NETS)

Primary endpoint: Progression Free Survival (n=204)

- Lanreotide Autogel vs. placebo
  - p=0.0002
  - HR=0.47 [95% CI: 0.30, 0.73]

**Peptide Receptor Radionuclide Therapy**

- **Retrospective Analysis**
  - Key Inclusion: Octreoscan positive, Karnofsky performance status >50%
  - 504 patients (1772 total treatments) → 310 patients available for analysis

- **Results**
  - Median Overall Survival = 46 months; Median Progression-free Survival = 33 months
  - Toxicities: Mostly acute and subacute (nausea, vomiting, abdominal pain, hair loss); rare serious delayed (renal insufficiency, liver toxicity, myelodysplastic syndrome)

**Responses 3 Months After Last Administration of $^{177}$Lu-Octreotate (n=310)**

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Response n (%)</th>
<th>Minor Response n (%)</th>
<th>Stable n (%)</th>
<th>Progressive n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinoid</td>
<td>42 (23)</td>
<td>31 (17)</td>
<td>78 (42)</td>
<td>37 (20)</td>
</tr>
<tr>
<td>Pancreas NET</td>
<td>30 (42%)</td>
<td>13 (18%)</td>
<td>19 (26%)</td>
<td>10 (14%)</td>
</tr>
<tr>
<td>Other</td>
<td>19 (38%)</td>
<td>7 (14%)</td>
<td>10 (20%)</td>
<td>14 (28%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>86 (28)</strong></td>
<td><strong>51 (16)</strong></td>
<td><strong>107 (35)</strong></td>
<td><strong>61 (20)</strong></td>
</tr>
</tbody>
</table>

Kwekkeboom, JCO, 2008; 2124.
Current Trial: PRRT with $^{177}\text{Lu-DOTA}$
Phase III: NETTER-1 Trial

1° endpoint PFS

Advanced, progressive, somatostatin receptor positive, midgut carcinoid tumours

$^{177}\text{Lu-DOTA}^0\text{-Tyr}^3\text{-Octreotate}$ + Octreotide LAR

Octreotide LAR 60 mg

Sponsor: Advanced Accelerator Applications, France

Future Attempts at Targeting SSTR:

- $^{177}\text{Lu-DOTA-JR11}$: SSTR2 antagonist
  -- Wolfgang Weber @ Memorial Sloan Kettering

- Nanoparticle delivery targeting SSTR2
  -- Herb Chen @ University of Wisconsin

- Adeno-associated viral construct targeting SSTR2
  -- Renata Pasquillini @ MD Anderson

- Immunologic targeting of SSTR2 with CAR-T cells
  -- David Metz et al @ University of Pennsylvania
Targeting the mTOR pathway

![Diagram showing the mTOR pathway and its effects on cancer cell and endothelial cell growth and proliferation.]  

Targeting mTOR in PNETs: Ph III Everolimus (RADIANT 3)

- **Advanced pancreatic NETs**  
  - n=410
  - Everolimus 10 mg qd  
  - N=207
  - Placebo  
  - N=203

  Median PFS  
  - Everolimus 11.0 mo  
  - Placebo 4.6 mo  
  - P<0.001

  FDA approved for Pancreatic NET

Yao. NEJM.2011.
Targeting mTOR in non-pancreatic NETs: Ph III Everolimus (RADIANT 2)

Advanced carcinoid 
\( \text{n=429} \)

\[ \rightarrow \]

R

<table>
<thead>
<tr>
<th>Arm</th>
<th>( \text{n=216} )</th>
<th>( \text{n=213} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Everolimus 10 mg + Octreotide LAR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo + Octreotide LAR</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PFS by Central Review

Best Percentage Change from Baseline

- Everolimus 16.4 mo
- Placebo 11.3 mo

Recently Completed Trial Targeting mTOR: Phase III RADIANT 4

1° endpoint Progression Free Survival [closed to accrual]

Advanced, progressive, somatostatin receptor positive, GI and lung carcinoid tumours

<table>
<thead>
<tr>
<th>Arm</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Everolimus + BSC</td>
<td></td>
</tr>
<tr>
<td>Best Supportive Care</td>
<td></td>
</tr>
</tbody>
</table>
Angiogenesis as a Target

Taking Advantage of Hypervascular Features of NETs
New blood vessels grow due to Receptor Mediated Signaling Pathway

Endothelial Cell

Flk-1/KDR (VEGFR-2)

Growth, Migration, Permeability, Anti-apoptosis

VEGF

Kinase Activation Cascade

VEGF-C, VEGF-D

Bevacizumab
New blood vessels grow due to Receptor Mediated Signaling Pathway

Endothelial Cell

Flk-1/KDR (VEGFR-2)

Growth, Migration, Permeability, Anti-apoptosis

VEGF

Kinase Activation Cascade

Aflibercept

Ramicurumab

Kinase Activation Cascade

Growth, Migration, Permeability, Anti-apoptosis
New blood vessels grow due to Receptor Mediated Signaling Pathway

Endothelial Cell

Kinase Activation Cascade

Growth, Migration, Permeability, Anti-apoptosis

Sunitinib
Sorafenib
Pazopanib
Axitinib, etc

VEGF

VEGF-C
VEGF-D

Barrier

CT Perfusion Scans


Bevacizumab effect on tumor blood flow

CT Perfusion Scans

Yao J, JCO, 2008: 1316.
Bevacizumab effect on tumor blood flow


CT Perfusion Scans

Stanford Cancer Center

Sunitinib vs Placebo in Pancreatic NET

*159 patients:
  • Well-differentiated
  • Progression in past 12 months

Sunitinib 37.5 mg/day orally, continuous daily dosing*

Placebo*

1:1

Primary endpoint: Progression Free Survival


Stanford Cancer Center
Sunitinib: Progression Free Survival

Estimate of median PFS:
- sunitinib: 11.1 months (95% CI: 7.4–NR)
- placebo: 5.5 months (95% CI: 3.5–7.4)
Hazard ratio 0.397 (95% CI: 0.243–0.649)
P<0.001

Carcinoid Trials targeting angiogenesis

Advanced, progressive carcinoids
SWOG Trial (Yao PI)

Bevacizumab + Octreotide LAR

Interferon + Octreotide LAR
Carcinoid Trials targeting angiogenesis

- Advanced, progressive carcinoids
  - Bevacizumab + Octreotide LAR
  - Interferon + Octreotide LAR
  - Closed to accrual

Alliance Trial (Bergsland PI)

Completed Trial Combining Targeted Agents: Everolimus +/- Bevacizumab

- Advanced, progressive pancreatic NETs
  - Everolimus + Octreotide LAR
  - Everolimus + Bevacizumab + Octreotide LAR

CALGB 80701 (Kulke PI): Phase II; 1° endpoint PFS

Sponsor: CALGB
Chemotherapy for NETs

Streptozocin

- Naturally occurring nitrosourea
- Initially identified in 1950’s as an antibiotic
- Found to be “selectively toxic” to beta cells of islets
- Approved by FDA for islet cell tumors in 1976

Streptozocin-based regimens

<table>
<thead>
<tr>
<th>Regimen</th>
<th>*N</th>
<th>Tumor Type</th>
<th>Response **Rate</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>STZ/5-FU vs. STZ/Dox</td>
<td>105</td>
<td>PNET</td>
<td>45% 69%</td>
<td>Moertal et al NEJM ‘92</td>
</tr>
<tr>
<td>***STZ/5-FU/Dox</td>
<td>84</td>
<td>PNET</td>
<td>39%</td>
<td>Kouvaraki et al JCO ‘04</td>
</tr>
<tr>
<td>STZ/Dox vs. Dox/5-FU</td>
<td>176</td>
<td>carcinoid</td>
<td>16% 16%</td>
<td>Sun et al JCO ‘05</td>
</tr>
<tr>
<td>STZ/5-FU vs. Interferon</td>
<td>64</td>
<td>carcinoid</td>
<td>3% 9%</td>
<td>Dahan et al Endocr Rel Ca ‘09</td>
</tr>
</tbody>
</table>

*Studies with > 20 patients
**Response criteria inconsistent
***Retrospective report
DTIC and Temozolomide

- Both are alkylators and share an active metabolite
- DNA adduct repaired by MGMT
  - Data from glioblastoma suggests MGMT deficient tumors predict for better response
- DTIC has single agent activity in NETs
  - PNET 33% response rate (Bukowski et al. Cancer ’94)
  - Carcinoid 8-16% response rate (Sun et al. JCO ’05)
- Temozolomide with better blood brain barrier penetration and greater convenience

Role of MGMT in Temozolomide Resistance

# MGMT expression and response to *Temozolomide in NETs*

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Tumor type</th>
<th>Radiologic Response (RECIST)</th>
<th>Biochemical Response (CGA)</th>
<th>Median PFS (months)</th>
<th>Median Survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MGMT +</td>
<td>16</td>
<td>3 pancreas 13 carcinoid</td>
<td>0/16</td>
<td>0/10</td>
<td>9.25</td>
<td>14</td>
</tr>
<tr>
<td>MGMT -</td>
<td>5</td>
<td>All pancreas</td>
<td>4/5**</td>
<td>4/5</td>
<td>19</td>
<td>Not reached</td>
</tr>
</tbody>
</table>

*MGMT intact tumor*  
*MGMT deficient tumor*

*Temozolomide was given in combination with either thalidomide or bevacizumab in separate phase II trial*  
**p<0.05**  

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# *Temozolomide-based Regimens*

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Tumor Type</th>
<th>Response Rate</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMZ</td>
<td>36</td>
<td>PNET Carcinoid</td>
<td>8% <strong>30%</strong></td>
<td>Ekeblad et al Clin Cancer Res ’07</td>
</tr>
<tr>
<td>TMZ + Thalidomide</td>
<td>29</td>
<td>PNET Carcinoid</td>
<td>45% 7%</td>
<td>Kulke et al JCO ’06</td>
</tr>
<tr>
<td>TMZ+Bev</td>
<td>34</td>
<td>PNET Carcinoid</td>
<td>24% 0%</td>
<td>Kulke, et al Clin Cancer Res ’09</td>
</tr>
<tr>
<td>TMZ + Capecitabine</td>
<td>33</td>
<td>PNET</td>
<td>67%</td>
<td>Strosberg, et al Cancer ’10</td>
</tr>
</tbody>
</table>

*Variety of dosing regimens used*  
**4 of 13 bronchial carcinoids responded (one was atypical); 3 of the 4 responding patients were deficient in MGMT*
Temozolomide-Based Therapy in Pancreatic NET

<table>
<thead>
<tr>
<th>Regimen</th>
<th>N</th>
<th>RR</th>
<th>TTP/PFS (mo.)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retrospective Series</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tem</td>
<td>12</td>
<td>8%</td>
<td>NR</td>
<td>Ekeblad, Clin Cancer Res, 2007</td>
</tr>
<tr>
<td>Tem/Capecitabine</td>
<td>30</td>
<td>70%</td>
<td>18</td>
<td>Strosberg, Cancer, 2011</td>
</tr>
<tr>
<td>Tem (various regimens)</td>
<td>53</td>
<td>34%</td>
<td>13.6</td>
<td>Kulke, Clin Cancer Res, 2009</td>
</tr>
<tr>
<td>Prospective Trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tem/Thalidomide</td>
<td>11</td>
<td>45%</td>
<td>NR</td>
<td>Kulke, JCO, 2006</td>
</tr>
<tr>
<td>Tem/Bevacizumab</td>
<td>15</td>
<td>33%</td>
<td>14.3</td>
<td>Chan, JCO, 2012</td>
</tr>
<tr>
<td>Tem/Everolimus</td>
<td>40</td>
<td>40%</td>
<td>15.4</td>
<td>Chan, Cancer, 2013</td>
</tr>
<tr>
<td>Tem/Capecitabine</td>
<td>11</td>
<td>36%</td>
<td>&gt;20</td>
<td>Fine, ASCO GI, 2014</td>
</tr>
</tbody>
</table>

*Data shown above limited to panc NET only, although studies may have included both pNET and carcinoid.

Trials in progress: Chemo Combination

ECOG 2211 (Kunz PI): Phase II, 1° endpoint PFS

Low and intermediate grade advanced pancreatic NETs → Temozolomide → Temozolomide / Capecitabine

R

MGMT will be assessed
Conclusions

- Management of NETs has changed over last 10 years
- Somatostatin analogues effective
- PRRT in randomized trial
- mTOR and angiogenesis validated targets
- Chemo can still be effective (predominantly in PNETs)
- First ever adjuvant trial open for resected liver mets