Cutting Edge Treatment of Neuroendocrine Tumors

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DISCLOSURE

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• On the Speakers Bureau for Lexicon
Neuroendocrine tumors (NETs)

**Definition:** Rare tumors arising from cells throughout the nervous and endocrine systems that may secrete regulatory hormones in response to signals from the nervous system.
Anatomical Distribution of NETs

• GI NETs
  – Duodenal, jejunal, ileal, colon
  – Appendix
  – Rectal
  – Gastric

• Thoracic NETs
  – Thymus
  – Lung (typical vs atypical lung carcinoid)

• Pancreas NETs (pNETs)
  – Nonfunctional
  – Gastrinoma
  – Insulinoma
  – Glucagonoma
  – VIPoma
Increased Incidence of NETs


[Graph showing the incidence of all malignant neoplasms and neuroendocrine tumors over time, with a clear increase in the incidence of neuroendocrine tumors.]
## NET Classifications

<table>
<thead>
<tr>
<th>Grade</th>
<th>Differentiation</th>
<th>GEP-NET Definition</th>
<th>WHO Classification</th>
<th>ENETS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>Well Differentiated</td>
<td>≤2% Ki-67 Index</td>
<td>Neuroendocrine Neoplasm Grade 1</td>
<td>TNM Grade 1 (G1)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Well Differentiated</td>
<td>3%-20% Ki-67 Index</td>
<td>Neuroendocrine Neoplasm Grade 2</td>
<td>TNM Grade 2 (G2)</td>
</tr>
<tr>
<td>High</td>
<td>Poorly Differentiated</td>
<td>&gt;20% Ki-67 Index</td>
<td>Neuroendocrine Carcinoma Grade 3</td>
<td>TNM Grade 3 (G3)</td>
</tr>
</tbody>
</table>
Therapies Used in NETs

• Surgery
• Liver Directed Therapy
• Systemic Therapies:
  – Somatostatin Analogs
  – Targeted Agents
  – Peptide Receptor Radionuclide Therapy
  – Chemotherapy
  – Clinical Trials
Resection of the Primary NET

Improves Survival with or without Liver Treatment

- OS Gastric without Liver Treatment
  - p = 0.1329

- OS Pancreas without Liver Treatment
  - P = 0.0002

- OS Small Bowel without Liver Treatment
  - p < 0.0001

- OS Colorectal without Liver Treatment
  - p < 0.0001

n= 864 Stage 4 California Cancer Registry

Radioembolization for NET liver Metastasis

- 34 patients with various NETs
- 50% radiographic responses observed:
  - 6 (18%) CR
  - 11 (32%) PR

### Table 1
Characteristics of Patients with Best Liver Response to Yttrium-90 Radioembolization by Response Evaluation Criteria in Solid Tumors

<table>
<thead>
<tr>
<th>CT Response in Liver</th>
<th>Primary Site</th>
<th>Prior Liver Treatments</th>
<th>Prior Extrahepatic Disease</th>
<th>% Hepatic Replacement</th>
<th>Follow-up, mo</th>
<th>SIR-Spheres Dose Delivered, GBq</th>
<th>Yttrium 90 Estimated Tumor Dose, Gy</th>
<th>CgA Fall, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>Pancreas</td>
<td>LR</td>
<td>Nil</td>
<td>30</td>
<td>42</td>
<td>1.9</td>
<td>79</td>
<td>-83</td>
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<tr>
<td>CR</td>
<td>Small bowel</td>
<td>LR</td>
<td>Nil</td>
<td>1</td>
<td>42</td>
<td>1.6</td>
<td>62</td>
<td>-63</td>
</tr>
<tr>
<td>CR</td>
<td>Small bowel</td>
<td>Nil</td>
<td>+</td>
<td>10</td>
<td>33</td>
<td>2</td>
<td>16</td>
<td>-48</td>
</tr>
<tr>
<td>CR</td>
<td>Medullary thyroid</td>
<td>Nil</td>
<td>Nil</td>
<td>50</td>
<td>48</td>
<td>2</td>
<td>46</td>
<td>-60</td>
</tr>
<tr>
<td>CR</td>
<td>Small bowel</td>
<td>Nil</td>
<td>Nil</td>
<td>10</td>
<td>28</td>
<td>0.9</td>
<td>19</td>
<td>-70</td>
</tr>
<tr>
<td>PR</td>
<td>Small bowel</td>
<td>Nil</td>
<td>Nil</td>
<td>60</td>
<td>26</td>
<td>2.3</td>
<td>18</td>
<td>-23</td>
</tr>
<tr>
<td>PR</td>
<td>Small bowel</td>
<td>Nil</td>
<td>Nil</td>
<td>50</td>
<td>4*</td>
<td>1.9</td>
<td>45</td>
<td>-31</td>
</tr>
<tr>
<td>PR</td>
<td>Small bowel</td>
<td>Nil</td>
<td>Nil</td>
<td>40</td>
<td>8*</td>
<td>1.9</td>
<td>60</td>
<td>-31</td>
</tr>
<tr>
<td>PR</td>
<td>Unknown</td>
<td>Nil</td>
<td>Nil</td>
<td>50</td>
<td>11*</td>
<td>2.3</td>
<td>40</td>
<td>-14</td>
</tr>
<tr>
<td>PR</td>
<td>Small bowel</td>
<td>IV</td>
<td>+</td>
<td>30</td>
<td>24*</td>
<td>1.9</td>
<td>Nil baseline</td>
<td>-68</td>
</tr>
<tr>
<td>PR</td>
<td>Pancreas</td>
<td>LR</td>
<td>Nil</td>
<td>10</td>
<td>45</td>
<td>1.5</td>
<td>65</td>
<td>-77</td>
</tr>
<tr>
<td>PR</td>
<td>Gucagonoma</td>
<td>Nil</td>
<td>Nil</td>
<td>10</td>
<td>41</td>
<td>2</td>
<td>125</td>
<td>-63</td>
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<tr>
<td>PR</td>
<td>Unknown</td>
<td>Nil</td>
<td>+</td>
<td>30</td>
<td>41</td>
<td>2.1</td>
<td>36</td>
<td>-20</td>
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<tr>
<td>PR</td>
<td>Unknown</td>
<td>Nil</td>
<td>+</td>
<td>20</td>
<td>35</td>
<td>1.6</td>
<td>55</td>
<td>-25</td>
</tr>
<tr>
<td>PR</td>
<td>Somatostatinoma</td>
<td>LR</td>
<td>Nil</td>
<td>10</td>
<td>39</td>
<td>1.8</td>
<td>50</td>
<td>-12.5</td>
</tr>
<tr>
<td>PR</td>
<td>Pancreas</td>
<td>Nil</td>
<td>+</td>
<td>25</td>
<td>29</td>
<td>2.1</td>
<td>61</td>
<td>-25</td>
</tr>
<tr>
<td>PR</td>
<td>Small bowel</td>
<td>Nil</td>
<td>Nil</td>
<td>40</td>
<td>12*</td>
<td>2</td>
<td>52</td>
<td>-55</td>
</tr>
<tr>
<td>SD</td>
<td>Bronchus</td>
<td>Nil</td>
<td>Nil</td>
<td>10</td>
<td>8</td>
<td>2</td>
<td>105</td>
<td>-55</td>
</tr>
<tr>
<td>SD</td>
<td>Small bowel</td>
<td>LR</td>
<td>+</td>
<td>20</td>
<td>20*</td>
<td>2.3</td>
<td>52</td>
<td>-86</td>
</tr>
<tr>
<td>SD</td>
<td>Small bowel</td>
<td>IV</td>
<td>+</td>
<td>50</td>
<td>39*</td>
<td>2.1</td>
<td>65</td>
<td>-79</td>
</tr>
<tr>
<td>SD</td>
<td>Vipoma</td>
<td>LR</td>
<td>+</td>
<td>20</td>
<td>18*</td>
<td>2.1</td>
<td>89</td>
<td>No change</td>
</tr>
<tr>
<td>SD</td>
<td>Small bowel</td>
<td>LR</td>
<td>+</td>
<td>25</td>
<td>24*</td>
<td>1.9</td>
<td>40</td>
<td>-75</td>
</tr>
</tbody>
</table>

King et al. Cancer 2008
Somatostatin Analog: Octreotide

PROMID

- Phase III, double blind, placebo controlled
- Well-differentiated, metastatic, midgut NETs
- Treatment naïve
- Octreotide LAR (n=42)
- Placebo (n=43)

Rinke A. et al. JCO 2009
Somatostatin Analog: Lanreotide

CLARINET

- Phase III, Randomized, double blind, placebo controlled
- Advanced, well-differentiated, nonfunctioning, somatostatin receptor positive, grade 1 or 2 NETs
- Pancreas, midgut, hindgut, or unknown origin
- Lanreotide (n=101)
- Placebo (n=103)

Caplin ME. et al. NEJM 2014
Treatment of Carcinoid Syndrome: Telotristat Ethyl

Inclusion:
- Patients with carcinoid syndrome not adequately controlled by somatostatin analogs

Double-Blind Treatment
- Placebo (n=45)
- Telotristat ethyl 250 mg (n=45)
- Telotristat ethyl 500 mg (n=45)

Bowel movement reduction
- $-1.4 \, T+SSA \, vs \, -0.6 \, SSA \, (p<0.001)$

Kulke M. et al. JCO. 2017
Targeted Agents: Everolimus

RADIANT 3

Inclusion:
- Low or Intermediate Grade
- Advanced Pancreatic NETs
- Progressive disease

Randomization 1:1
- Everolimus 10mg Daily + Octreotide 30mg LAR
- Placebo + Octreotide 30mg LAR

N=410

Kaplan–Meier median
Everolimus, 11.4 mo
Placebo, 5.4 mo
Hazard ratio, 0.34 (95% CI, 0.26–0.44)
P<0.001 by one-sided log-rank test

Yao J. NEJM 2011
Targeted Agents: Everolimus

RADIANT 4

Inclusion:
- Well-Differentiated Advanced NETs
- Lung or GI Origin
- Progressive Disease
- Non-functional

Randomization 2:1
- Everolimus 10mg Daily
- Placebo

Kaplan-Meier median progression-free survival
Everolimus 11.0 months (95% CI 9.2–13.3)
Placebo 3.9 months (95% CI 3.6–7.4)
HR 0.48 (95% CI 0.35–0.67)
p<0.00001 by stratified one-sided log-rank test

Yao J. Lancet 2016
Targeted Agents: Sunitinib

Phase III, Double-Blind, Placebo Controlled Trial

Inclusion:
- Well-differentiated, advanced PNETs

Randomized 1:1
- Sunitinib 37.5 mg/daily (n=86)
- Placebo (n=85)

Median PFS
- Sunitinib: 11.4 Months
- Placebo: 5.5 Months

Raymond E. NEJM 2011
Peptide Receptor Radionucleotide Therapy

177Lu-Dotatate: Mechanism of Action
**Peptide Receptor Radionucleotide Therapy**

**NETTER-1**

**Inclusion:**
- Well-differentiated, metastatic midgut neuroendocrine tumors

**Randomized 1:1**
- 177Lu-Dotatate at a dose of 7.4 GBq plus Octreotide LAR 30 mg (n=116)
- Octreotide LAR alone at 60mg (n=113)

**Median PFS**
- 177Lu-Dotatate Group: Not Reached
- Control Group: 8.4 months

Strosberg J. NEJM 2017
# Chemotherapy in Metastatic NETs (Predominately PNETs)

<table>
<thead>
<tr>
<th>Regimen</th>
<th># of Patients</th>
<th>Tumor response rate, percent</th>
<th>Median PFS months</th>
<th>Median OS, months</th>
<th>Author, year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluorouracil + streptozocin</td>
<td>33</td>
<td>45†</td>
<td>14</td>
<td>16.8</td>
<td>Moertel C; 1992</td>
</tr>
<tr>
<td>Doxorubicin + streptozocin</td>
<td>36</td>
<td>69†</td>
<td>18</td>
<td>26.4</td>
<td></td>
</tr>
<tr>
<td>Dacarbazine (DTIC)</td>
<td>50</td>
<td>34</td>
<td>NR</td>
<td>19.3</td>
<td>Ramanathan R; 2001</td>
</tr>
<tr>
<td>Temozolomide + thalidomide</td>
<td>11</td>
<td>45</td>
<td>NR</td>
<td>NR</td>
<td>Kulke M; 2006</td>
</tr>
<tr>
<td>Temozolomide + bevacizumab</td>
<td>15</td>
<td>33</td>
<td>14.3</td>
<td>41.7</td>
<td>Chan JA; 2012</td>
</tr>
<tr>
<td>Temozolomide + everolimus</td>
<td>40</td>
<td>40</td>
<td>15.4</td>
<td>NR</td>
<td>Chan JA; 2013</td>
</tr>
<tr>
<td>Temozolomide + capecitabine</td>
<td>11</td>
<td>36</td>
<td>&gt;20</td>
<td>&gt;24.4</td>
<td>Fine RL; 2014</td>
</tr>
</tbody>
</table>

† Combined biochemical and radiologic response rate.
Randomized phase II: Unresectable, G1 or G2 PNETs
Primary endpoint: Median PFS 22.7 months for TC vs 14.4 months for T (HR 0.58, p=0.023)
Median OS: 38 months for T versus not reached for TC (HR=0.41, p=0.012)
## ECOG 2211: Response Rates

<table>
<thead>
<tr>
<th>Status</th>
<th>Temozolomide (N=72)</th>
<th>Temozolomide + Capecitabine (N=72)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>2.8%</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Partial response</td>
<td>25.0%</td>
<td>33.3%</td>
<td></td>
</tr>
<tr>
<td>Stable disease</td>
<td>40.3%</td>
<td>48.6%</td>
<td></td>
</tr>
<tr>
<td>Progressive disease</td>
<td>19.4%</td>
<td>13.9%</td>
<td></td>
</tr>
<tr>
<td>Unevaluable</td>
<td>12.5%</td>
<td>4.2%</td>
<td></td>
</tr>
<tr>
<td><strong>Objective Response Rate (CR+PR)</strong></td>
<td>27.8%</td>
<td>33.3%</td>
<td>0.47</td>
</tr>
<tr>
<td><strong>Disease Control Rate (CR+PR+SD)</strong></td>
<td>68.1%</td>
<td>81.9%</td>
<td></td>
</tr>
<tr>
<td><strong>Response Duration (median)</strong></td>
<td>9.7 mo</td>
<td>12.1 mo</td>
<td></td>
</tr>
</tbody>
</table>
Select Ongoing Clinical Trials

• Targeted Therapy
  – Cabozantinib (VEGF, MET)
  – Sulfatinib (VEGF, FGF)
• Immunotherapy
  – PDR001: PD-1 Immune Checkpoint Inhibition (Presentation at ESMO 2018)
  – XmAb18087: Bispecific Tumor Targeting Ab (SSTR2 and CD3)
• PRRT
  – SSTR Antagonist: 177Lu-OPS201
  – Alpha Emitters: 212 Pb-AR-RMX
  – COMPETE: 177Lu-edotretotide vs everolimus
• Combination Therapies
  – CONTROL NETS: Cape/Tem+177Lu-Octreotate vs Cape/Tem
Primary endpoint: RECIST response rates
Secondary endpoints: Progression free and overall survival, safety and toxicity

Chan J. GI ASCO 2017
Pancreatic NET: RECIST Response Profile

<table>
<thead>
<tr>
<th>Response</th>
<th>N=20</th>
<th>% (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR</td>
<td>3</td>
<td>15% (5-36%)</td>
</tr>
<tr>
<td>SD</td>
<td>15</td>
<td>75% (53-89%)</td>
</tr>
<tr>
<td>Unknown*</td>
<td>2</td>
<td>10% (3-30%)</td>
</tr>
</tbody>
</table>

* Treatment stopped prior to restaging.
Carcinoid: RECIST Response Profile

<table>
<thead>
<tr>
<th>Response</th>
<th>N</th>
<th>% (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR</td>
<td>6</td>
<td>15% (7-28%)</td>
</tr>
<tr>
<td>SD</td>
<td>26</td>
<td>63% (48-76%)</td>
</tr>
<tr>
<td>PD</td>
<td>2</td>
<td>5% (1-16%)</td>
</tr>
<tr>
<td>Unknown*</td>
<td>7</td>
<td>17% (9-31%)</td>
</tr>
</tbody>
</table>

* Treatment stopped prior to restaging.
ALLIANCE A021602: CABINET
Phase III trial in patients with advanced NETs after progression on everolimus

**Schema**
1 Cycle = 28 Days

Pancreatic NET → Randomize * → 2:1 → Carcinoid Tumor

* Randomization will be done separately for the pancreatic NET and carcinoid tumor cohorts.

Cabozantinib 60mg daily **

Placebo 60mg daily **

** Treatment is to continue until disease progression, unacceptable toxicity, or withdrawal of consent. Patients will be followed for survival and progression every 12 weeks until progression or start of new anticancer therapy, and then for survival every 6 months until 8 years after registration or until death, whichever comes first.
An Open-Label Phase Ib/II Study of Sulfatinib in Patients with Advanced Neuroendocrine Tumors
(NCT02267967)

J.M. Xu\textsuperscript{a}, J. Li\textsuperscript{b}, C.M. Bai\textsuperscript{c}, N. Xu\textsuperscript{d}, Z.W. Zhou\textsuperscript{e}, Z.P. Li\textsuperscript{f}, C.C. Zhou\textsuperscript{g}, W. Wang\textsuperscript{h}, J. Li\textsuperscript{h}, C. Qi\textsuperscript{h}, Y. Hua\textsuperscript{h}, W.G. Su\textsuperscript{h}.

\textsuperscript{a}The 307\textsuperscript{th} Hospital of Chinese People's Liberation Army, Beijing, China; \textsuperscript{b}Beijing Cancer Hospital, Beijing, China; \textsuperscript{c}Peking Union Medical College Hospital, Beijing, China; \textsuperscript{d}The First Affiliated Hospital of Zhejiang University, Hangzhou, China; \textsuperscript{e}Sun Yat-sen University Cancer Center, Guangzhou, China; \textsuperscript{f}West China Hospital, Sichuan University, Chengdu, China; \textsuperscript{g}Shanghai Pulmonary Hospital, School of Medicine, Tongji University, Shanghai, China; \textsuperscript{h}Hutchison MediPharma Limited, Shanghai, China.
**Sulfatinib phase Ib/II study in G1/2 NET SANET-1**

**Study population:**
- ECOG PS 0 or 1.
- Measurable disease.
- Unresectable or metastatic NET.
- Grade 1 or 2.
- Failed standard therapy or standard therapy unavailable.

**Continuous treatment in 28-day cycles, until:**
- Disease progression.
- Unacceptable toxicity.
- Other reasons.

**Single arm sulfatinib 300mg QD p.o.**

**Primary Endpoints:** ORR and safety (CTC AE 4.03).

**Secondary Endpoints:** DCR, DoR and PFS (RECIST1.1) and PK characteristics.
<table>
<thead>
<tr>
<th>Treatment</th>
<th>N=41</th>
<th>n (%)</th>
<th>PR (confirmed)</th>
<th>7 (17.1%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>SD</td>
<td>30 (73.2%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PD</td>
<td>1 (2.4%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NE*</td>
<td>3 (7.3%)</td>
</tr>
<tr>
<td>ORR (95% CI)</td>
<td></td>
<td></td>
<td>17.1%</td>
<td>(7.2%-32.1%)</td>
</tr>
<tr>
<td>DCR (95% CI)</td>
<td></td>
<td></td>
<td>90.2%</td>
<td>(76.9%-97.3%)</td>
</tr>
<tr>
<td>PNET</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EP-NET</td>
<td>N=40</td>
<td>n (%)</td>
<td>PR (confirmed)</td>
<td>6 (15.0%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>SD</td>
<td>31 (77.5%)</td>
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<td></td>
<td></td>
<td></td>
<td>PD</td>
<td>1 (2.5%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NE*</td>
<td>2 (5.0%)</td>
</tr>
<tr>
<td>ORR (95% CI)</td>
<td></td>
<td></td>
<td>15.0%</td>
<td>(5.7%-29.8%)</td>
</tr>
<tr>
<td>DCR (95% CI)</td>
<td></td>
<td></td>
<td>92.5%</td>
<td>(79.6%-98.4%)</td>
</tr>
</tbody>
</table>

*NE: not evaluable

Best percent change from baseline of target lesions in evaluable pts (%)

PNET group

EP-NET group

14th Annual ENETS Conference | 8-10 March 2017 | 28
Immunotherapy: Bi-Specific Tumor Targeting Antibody

Abbreviations: Fc=fragment, crystallizable; scFv=single-chain variable fragment (immunoglobulin fusion protein); SSTR=somatostatin receptor
PRRT with SSTR antagonists:
1) Binding independent of somatostatin receptor activation state
2) Potential to occupy more binding sites on tumor cell surface

68Ga-DOTATATE PET images of patient 2 before (A) and 3 mo after (B) treatment with 15.2 GBq of 177Lu-DOTA-JR11 and 68Ga-DOTATATE PET images of patient 3 before (C) and 12 mo after (D) treatment with 5.9 GBq of 177Lu-DOTA-JR11. Damian Wild et al. J Nucl Med 2014;55:1248-1252
Thank You