Recent developments of oncology in neuroendocrine tumors (NETs)

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## Disclosures

<table>
<thead>
<tr>
<th>Category</th>
<th>Companies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advisory Board</td>
<td>Amgen, Bayer, IMS health, Ipsen, Sanofi, Shire, Sirtex</td>
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<td>Speakers Fee</td>
<td>Amgen, Bayer, MerckSerono, Sanofi, Servier, Sirtex</td>
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<tr>
<td>Scientific Grants</td>
<td>Amgen, Bayer, Ipsen, Novartis, Roche</td>
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### Strategy in NET – diagnostic work-up

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</thead>
<tbody>
<tr>
<td>Benign</td>
<td>Well-differentiated endocrine tumor</td>
<td>NET G1 or NET G2</td>
<td>-</td>
<td>-</td>
<td>≤2</td>
<td>-</td>
<td>usually around 2</td>
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<tr>
<td>Benign or low-grade malignant</td>
<td>Well-differentiated endocrine tumor</td>
<td>NET G1 or NET G2</td>
<td>-</td>
<td>-</td>
<td>&gt;2</td>
<td>±</td>
<td>usually around 2</td>
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<tr>
<td>Low-grade malignant</td>
<td>Well-differentiated endocrine carcinoma</td>
<td>NET G1 or G2</td>
<td>+</td>
<td>+</td>
<td>any</td>
<td>+</td>
<td>usually &gt;2</td>
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<tr>
<td>High-grade malignant</td>
<td>Poorly-differentiated endocrine carcinoma</td>
<td>NEC or G3</td>
<td>+</td>
<td>+</td>
<td>any</td>
<td>+</td>
<td>&gt;20</td>
</tr>
</tbody>
</table>

NET = Neuroendocrine tumor; NEC = neuroendocrine carcinoma.

ENETS Consensus Guidelines Neuroendocrinology 2012;95:120-134

Baum RP et al. Theranostics 2012;2:437-447
- Strategy in NET – multi Optional, disciplinary

<table>
<thead>
<tr>
<th>SURGERY</th>
<th>ORGAN DIRECTED</th>
<th>SYSTEMIC</th>
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<tbody>
<tr>
<td>primary tumor</td>
<td>RFA, RadioFrequencyAblation</td>
<td>chemotherapy</td>
</tr>
<tr>
<td>metastasis</td>
<td>chemoembolisation</td>
<td>‘target’ therapy</td>
</tr>
<tr>
<td></td>
<td>drug eluting beads</td>
<td></td>
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<tr>
<td></td>
<td>radioembolisation</td>
<td>immune therapy</td>
</tr>
<tr>
<td></td>
<td>$\text{P}^\text{eptide R} \text{eceptor R} \text{adionuclide T} \text{herapy}$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(tomo) radiation</td>
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Current therapeutic strategy in non-pancreatic NET

- Carcinoid syndrome
- Tumor control
- Somatostatin analogues
- Everolimus
- Disease progression
  - Regional therapy
  - PRRT
  - Study drugs
**PROMID – randomized, multicentric**

**HR** = 0.34 [95% CI: 0.20–0.59], *p* = 0.000072

- **Sandostatine LAR:** 42 patients / 26 events
  - Median **14.3 months** [95% CI: 11.0–28.8]

- **Placebo:** 43 patients / 40 events
  - Median **6.0 months** [95% CI: 3.7–9.4]
In summary, lanreotide was associated with prolonged progression-free survival among patients with advanced, grade 1 or 2 (Ki-67 <10%) enteropancreatic, somatostatin receptor-positive neuroendocrine tumors with prior stable disease, irrespective of the hepatic tumor volume.
Efficacy and Safety of Telotristat Ethyl in Patients With Carcinoid Syndrome Inadequately Controlled by Somatostatin Analogs: Analysis of the Completed TELESTAR Extension Period

3- to 4-week run-in (n=135) → 1:1:1 R → DBT Period
- Placebo tid (n=45)
- Telotristat ethyl 250 mg tid (n=45)
- Telotristat ethyl 500 mg tid (n=45)

OLE Period
- Telotristat ethyl 500 mg tid (n=115)

Evaluation of primary endpoint:
- Reduction in number of daily BMs from baseline (averaged over the 12-week DBT period)

All patients were required to be on long-acting SSA at enrollment and continue SSA therapy throughout the treatment period.
Efficacy and Safety of Telotristat Ethyl in Patients With Carcinoid Syndrome Inadequately Controlled by Somatostatin Analogs: Analysis of the Completed TELESTAR Extension Period
Midgut NEN

Pavel et al. Neuroendocrinology 2016;103:172-185
Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): a randomised, placebo-controlled, phase 3 study


Everolimus in combination with octreotide improves PFS in patients with advanced NET associated with carcinoid syndrome, regardless of previous SSA exposure

Efficacy of Everolimus Plus Octreotide LAR in Patients With Advanced Neuroendocrine Tumor and Carcinoid Syndrome: Final Overall Survival From the Phase 3 RADIANT-2 Study

Marianne E Pavel, Eric Baudin, Kjell E Öberg, John D Hainsworth, Maurizio Voi, Nicolas Rouyrre, Marc Peeters, David Gross, James C Yao
Pancreatic NET

Hormonal syndrome

Somatostatin analogues

Everolimus

Sunitinib

Chemotherapy

Somatostatin analogues?

Tumor control

Regional therapy

PRRT

Study drugs

Disease progression
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., Tomas 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

Kaplan–Meier median

Everolimus, 11.0 mo
Placebo, 4.6 mo

Hazard ratio, 0.35 (95% CI, 0.27–0.45)
P<0.001 by one-sided log-rank test

Probability of Progression-free Survival (%)

Censoring times
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Everolimus 10mg N = 207, n (%)</th>
<th>Placebo N = 203, n (%)</th>
</tr>
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<tbody>
<tr>
<td>Complete response (CR)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Confirmed partial response (PR)</td>
<td>10 (4.8)</td>
<td>4 (2.0)</td>
</tr>
<tr>
<td>Stable disease (SD)</td>
<td>151 (72.9)</td>
<td>103 (50.7)</td>
</tr>
<tr>
<td>Progressive disease (PD)</td>
<td>29 (14.0)</td>
<td>85 (41.9)</td>
</tr>
<tr>
<td>Unknown</td>
<td>17 (8.2)</td>
<td>11 (5.4)</td>
</tr>
<tr>
<td>Two-sided P-value for treatment difference*</td>
<td>P &lt; 0.0001</td>
<td></td>
</tr>
<tr>
<td>Disease control rate (CR + PR +SD)</td>
<td>161 (77.7)</td>
<td>107 (52.7)</td>
</tr>
</tbody>
</table>

Sunitinib Malate for the Treatment of Pancreatic Neuroendocrine Tumors

Eric Raymond, M.D., Ph.D., Laetitia Dahan, M.D., Ph.D., Jean-Luc Raoul, M.D., Ph.D., Yung-Jue Bang, M.D., Ivan Borbath, M.D., Ph.D., Catherine Lombard-Bohas, M.D., Juan Valle, M.D., Peter Metrakos, M.D., C.M., Denis Smith, M.D., Aaron Vinik, M.D., Ph.D., Jen-Shi Chen, M.D., Dieter Hörsch, M.D., Pascal Hammel, M.D., Ph.D., Bertram Wiedenmann, M.D., Ph.D., Eric Van Cutsem, M.D., Ph.D., Shem Patyna, Ph.D., Dongrui Ray Lu, M.Sc., Carolyn Blanckmeister, Ph.D., Richard Chao, M.D., and Philippe Ruszniewski, M.D.

Hazard ratio, 0.42 (95% CI, 0.26–0.66)  
P < 0.001

(11.4 vs. 5.5 mos)

Probability of Progression-free Survival (%)
Interferon-α was introduced for the treatment of carcinoid tumors by Oberg et al. in 1983

Immune therapy ‘avant la lettre’

- T-cell activation
- Anti-proliferative, anti-angiogenic, cytotoxic, apoptotic

Alonso-Gordoa, 2015
All studies were too small to show a statistically significant advantage

A heterogeneous patient population
US Boxed Warning

- May cause or aggravate severe neuropsychiatric adverse events; monitor closely with clinical evaluations (periodic); discontinue treatment for severe persistent or worsening symptoms; some cases may resolve with discontinuation.

- May cause or aggravate fatal or life-threatening autoimmune disorders (<6%); monitor closely with clinical and laboratory evaluations (periodic); discontinue treatment for severe persistent or worsening symptoms; some cases may resolve with discontinuation.

- May cause or aggravate fatal or life-threatening infectious disorders (<6%); monitor closely with clinical and laboratory evaluations (periodic); discontinue treatment for severe persistent or worsening symptoms; some cases may resolve with discontinuation.

- May cause or aggravate fatal or life-threatening ischemic disorders (<6%); monitor closely with clinical and laboratory evaluations (periodic); discontinue treatment for severe persistent or worsening symptoms; some cases may resolve with discontinuation.
PRINCIPLES OF SYSTEMIC ANTI-TUMOR THERAPY
Unresectable and/or Metastatic Neuroendocrine Tumors of the Gastrointestinal Tract, Lung, and Thymus (Carcinoid Tumors)

- Systemic therapy may not be appropriate for every patient with unresectable or metastatic disease. Consider multidisciplinary discussion to determine the best choice of treatment, including: observation for patients with stable disease with mild tumor burden, hepatic regional therapy for patients with liver predominant metastases, cytoreductive surgery, or systemic therapy may be appropriate considerations.
- Currently, there are no data to support a specific sequence of regional versus systemic therapy, and no data to guide sequencing of the following systemic therapy options.
- There is no known role for systemic treatment in the adjuvant setting for carcinoid tumors.
- Doses and schedules are subject to appropriate modifications depending on the circumstances.
- For management of hormone-related symptoms, see NET-6.

Systemic Treatment Options for Unresectable and/or Metastatic Neuroendocrine Tumors of the Gastrointestinal Tract, Lung, and Thymus (Carcinoid Tumors)

- Somatostatin analogues (somatostatin analog dosing also applicable for locoregional disease)
  - Octreotide® LAR 20–30 mg intramuscular injection, monthly
  - Lanreotide 120 mg deep subcutaneous injection, monthly

- Consider the following systemic therapies (listed in alphabetical order)
  - Cytotoxic chemotherapy (all category 3): Anticancer agents such as 5-fluorouracil (5-FU), capecitabine, dacarbazine, oxaliplatin, streptozocin, and temozolomide can be used in patients with progressive metastases for whom there are no other treatment options. (See Discussion for details.)
  - Everolimus³ (category 3)
  - Interferon alfa-2b⁴ (category 3)

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

*For symptom control, octreotide 150–250 mcg SC TID or octreotide LAR 20–30 mg IM every 4 weeks. Dose and frequency may be further increased for symptom control as needed. Therapeutic levels of octreotide would not be expected to be reached for 10–14 d after LAR injection. Short-acting octreotide can be added to octreotide LAR for rapid relief of symptoms or for breakthrough symptoms.

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Chemotherapy in NET – ‘carcinoma’ behavior

In summary, the combination of **capecitabine and temozolomide** is associated with an exceptionally promising objective response rate and overall survival duration in metastatic PECAs. Toxicity rates are considerably lower than those observed with streptozocin-based regimens. Future prospective trials should evaluate temozolomide monotherapy versus the combination of capecitabine and temozolomide to clinically test the hypothesized synergy between these two agents. Randomized clinical trials comparing temozolomide versus streptozocin-based regimens are also necessary to establish a standard of care for this rare malignancy.

Immunotherapy in NETs

KEYNOTE-028 (NCT02054806): Phase 1b Multicohort Study of Pembrolizumab for PD-L1+ Advanced Solid Tumors

- Patients
  - Carcinoid tumors or well or moderately differentiated pNETs
  - Failure of or inability to receive standard therapy
  - ECOG PS 0 or 1
  - \( \geq 1 \) measurable lesion
  - PD-L1 positivity\(^a\)
  - No autoimmune disease or interstitial lung disease

- Pembrolizumab 10 mg/kg IV Q2W

- CR, PR, or SD

- Treat for 24 months\(^b\) or until progression\(^c\) or intolerable toxicity

\(^a\) Response Assessment

Mehnert J et al. ESMO2017, A4270
Immunotherapy in NETs

PD-L1 Screening: Carcinoid/pNET Cohorts

Mehnert J et al. ESMO2017, A4270
- Immunotherapy in NETs

**Carcinoid**

**pNET**

- Discontinued, responder
- Ongoing, responder
- Discontinued, nonresponder
- Ongoing, nonresponder

Mehnert J et al. ESMO2017, A4270
- Palbociclib – CDK-inhibitor

**WATERFALL PLOT FOR RESPONSE**

Investigator-assessed maximum percent reduction in tumor lesions

Grande Pulido E et al. ESMO2017, A4290
Subtyping in panNETs – the way forward...

### Molecular Advances: Subtyping in panNETs

PanNETassigner signature developed using an integrated analysis of gene expression (221 genes), microRNA (30 miRs) and mutations (targeted mutational profiles of MEN1, DAXX/ATRX, TSC2, PTEN and ATM)

- **3 molecular subtypes identified**
  1. Metastases-like primary (MLP)
  2. Insulinoma-like (Ins)
  3. Intermediate (Int)

<table>
<thead>
<tr>
<th>Human PanNET</th>
<th>MLP (~38%)</th>
<th>Insulinoma (~25%)</th>
<th>Intermediate (~37%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Functional</td>
<td>Functional</td>
<td>Non-Functional</td>
<td></td>
</tr>
<tr>
<td>High Metastatic Potential</td>
<td>Low Metastatic Potential</td>
<td>Moderate Metastatic Potential</td>
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</tr>
<tr>
<td>Grade 1/2/3</td>
<td>Grade 1/2</td>
<td>Grade 1/2</td>
<td></td>
</tr>
<tr>
<td>DAXX, ATRX, TSC2, PTEN and ATM mutations</td>
<td>TSC2, PTEN and ATM mutations</td>
<td>MEN1 mutations</td>
<td></td>
</tr>
</tbody>
</table>

*Sadanandam A et al. Cancer Discov. 2015 Dec;5(12):1296-313*
• Overcome the resistance – thé way forward…

• Resistance induced in two pancreatic NET cell lines
• Analysis of resistant vs. non-resistant cell lines
  Whole exome sequencing
  19 genetic variants implicated in resistance
• Resistance can be overcome with new targeted drugs

Vandamme T et al.
NETwerk